Hyperglycemia in Extremely Preterm Infants—Insulin Treatment, Mortality and Nutrient Intakes

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Objective To explore the prevalence of hyperglycemia and the associations between nutritional intakes, hyperglycemia, insulin treatment, and mortality in extremely preterm infants.

Study design Prospectively collected data from the Extremely Preterm Infants in Sweden Study (EXPRESS) was used in this study and included 580 infants born <27 gestational weeks during 2004-2007. Available glucose measurements (n = 9850) as well as insulin treatment and nutritional data were obtained retrospectively from hospital records for the first 28 postnatal days as well as 28- and 70-day mortality data.

Results Daily prevalence of hyperglycemia >180 mg/dL (10 mmol/L) of up to 30% was observed during the first 2 postnatal weeks, followed by a slow decrease in its occurrence thereafter. Generalized additive model analysis showed that increasing parenteral carbohydrate supply with 1 g/kg/day was associated with a 1.6% increase in glucose concentration ($P < .001$). Hyperglycemia was associated with more than double the 28-day mortality risk ($P < .01$). In a logistic regression model, insulin treatment was associated with lower 28- and 70-day mortality when given to infants with hyperglycemia irrespective of the duration of the hyperglycemic episode ($P < .05$).

Conclusions Hyperglycemia is common in extremely preterm infants throughout the first postnatal month. Glucose infusions seem to have only a minimal impact on glucose concentrations. In the EXPRESS cohort, insulin treatment was associated with lower mortality in infants with hyperglycemia. Current practices of hyperglycemia treatment in extremely preterm infants should be reevaluated and assessed in randomized controlled clinical trials. *(J Pediatr 2018;■■:■■-■■).*

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Extremely preterm infants are prone to disturbances in glucose homeostasis. During the first postnatal week, about one-third of very low birth weight infants (<1500 g) have glucose concentrations of >180 mg/dL (10 mmol/L).[1-3] Few studies have focused on later weeks, although some recent studies suggest that extremely preterm infants may experience frequent hyperglycemia episodes nearing the time of discharge.[4,5]

There is no established definition of hyperglycemia in extremely preterm infants and various cut-offs have been used by different authors.[6] This, in combination with the lack of evidence of clinical benefit of insulin treatment, are likely reasons for the marked differences in clinical hyperglycemia management in preterm infants observed between different neonatal units and different countries.[7] Nevertheless, hyperglycemia in the early period of life of the preterm infant has been associated with a range of morbidity and mortality outcomes.[8-15]

We sought to describe the trends in plasma glucose concentrations in extremely preterm infants during the first 28 postnatal days and to assess possible associations between plasma glucose concentrations, nutritional intakes, insulin treatment, and neonatal mortality. We hypothesized that hyperglycemia would be observed frequently beyond the first postnatal week, that glucose infusions

CRIB	Clinical risk index
EXPRESS	Extremely Preterm Infants in Sweden Study
IVH	Intraventricular hemorrhage
NEC	Necrotizing enterocolitis
SGA	Small for gestational age

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would account for most of the variability in glucose concentrations, and that insulin treatment would be associated with lower mortality in hyperglycemic infants.

Methods

We used data from the Extremely Preterm Infants in Sweden Study (EXPRESS), a population-based cohort including all infants born at gestational age <27 completed weeks during a 3-year period between April 1, 2004 and March 31, 2007. Cohort characteristics, nutritional intakes, perinatal and growth outcomes, as well as survival and morbidity outcomes have been previously published.[16-18]

In total, 707 live-born infants were included in the study. We excluded 105 infants who did not survive the first 24 hours of life, 14 infants for whom perinatal data could not be retrieved, and 8 infants with congenital malformations involving the gut or multiple malformations or chromosomal aberrations. For the analysis of the association between hyperglycemia during 2 and 3 consecutive days, insulin treatment and mortality, we further excluded infants who did not survive the first 48 and 72 hours of life (n = 11 and 23), respectively.

The study was approved by the regional ethical committee in Lund, Sweden (Dnr 42/2004 and 138/2008), and written informed consent was obtained from all parents before or shortly after the child's birth. Clinical data was extracted from the EXPRESS database. Every available plasma glucose measurement was retrospectively obtained from hospital records for the first 28 postnatal days. Daily highest and lowest plasma glucose values were registered. If only 1 glucose value was available for a specific day, it was classified as both highest and lowest. Day zero was defined as lasting from the time of birth until next midnight. Following days were defined as calendar days. The vast majority of glucose measurements were analyzed out of plasma samples using different blood gas analyzers available at all neonatal care units (most common system: Radiometer, Brønshøj, Denmark). The glucose values were registered regardless of the origin of the blood sample (capillary, venous, or arterial). Measurements were excluded when samples were taken from a venous line with an ongoing glucose infusion.

Insulin treatment data was collected, when available, including type of preparation given, mode of treatment, concentration, dosage as well as total dose administered, and maximum infusion rate for each day of treatment. During the study period, there were no national guidelines for insulin treatment and for the most part no local guidelines were in use either in this population. Insulin treatment was given according to clinical judgement. Nutritional data was retrospectively collected as previously described.[18,19] Daily data was collected from hospital records regarding enteral and parenteral intakes of macronutrients (carbohydrates, protein, and fat; g/kg/day) until postnatal day 28. Nutritional and biochemical markers data were collected and stored using a computerized system (Nutrium software; Nutrium AB, Umeå, Sweden). Small for gestational age (SGA) was defined as birth weight below the 10th percentile for the general population.

Statistical Analyses

Data were analyzed by using SPSS statistical software v 24.0 for Windows (SPSS, Chicago, Illinois) and R v 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria). Hyperglycemia was defined as a highest plasma glucose value measurement >180 mg/dL (10 mmol/L) on a given day, unless otherwise specified.

To assess possible attrition bias because of discontinuation of plasma glucose monitoring in infants without hyperglycemia before reaching the age of 28 postnatal days, the Student *t* test was used to compare the frequency of glucose testing in 2 subgroups: (1) infants who were treated at 1 university hospital (hospital A) where the clinical practice was to perform plasma glucose measurements on a daily basis and (2) infants treated at the other university hospitals (hospitals B-G). Frequency of glucose testing was compared on a weekly basis among surviving infants in the respective week. Rates of hyperglycemia were compared between the groups using a χ^2 test.

To evaluate a possible association between nutritional intakes and plasma glucose concentrations, generalized additive models were used including a random effect for each patient, and a smooth spline adjusting for an average time trend in observed glucose concentrations. Thus, the analyses aimed to evaluate how daily nutritional intakes given to the infants influence glucose levels the following day during the first 28 postnatal days. Days where insulin treatment was given were excluded from these analyses. The glucose concentrations were log transformed (natural logarithm) to obtain Gaussian distributed data, and all models were adjusted for birth weight and gestational age. The relative effect of daily macronutrient intake (carbohydrates, protein, and fat) on glucose concentrations was analyzed separately for each macronutrient's parenteral, enteral, and total intake, and in a combined model to evaluate the effect of intake of all macronutrients together. A model including the total carbohydrate intake, number of culture-verified sepsis events during the first 28 postnatal days and duration (in days) of antibiotics treatment during the same period was used to account for a possible effect of sepsis events on glucose concentrations.

Possible associations between hyperglycemia, insulin treatment and 28- and 70-day mortality were analyzed in logistic regression models, adjusted for gestational age and birth weight. In the analyses of insulin treatment and mortality, hyperglycemia was defined using different approaches—a glucose concentration measurement >180 mg/dL (10 mmol/L), or >216 mg/dL (12 mmol/L), on 1 single day, or during 2 or 3 consecutive days during the first 28 postnatal days (12 separate analyses in total).

To account for differences in local treatment routines, we divided the entire cohort into 2 groups: region group 1—where insulin was given more often (treatment rate ≥20%; n = 314; 4 university hospitals) and region group 2—where insulin treatment was sparse (treatment rate <20%; n = 266; 3 university hospitals). An analysis of 28- and 70-day mortality in infants

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