Early Enhanced Parenteral Nutrition, Hyperglycemia, and Death Among Extremely Low-Birth-Weight Infants

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IMPORTANCE Efforts to optimize early parenteral nutrition (PN) in extremely low-birth-weight (ELBW) infants to promote growth and development may increase hyperglycemia risk. Recent studies have identified an association between early hyperglycemia and adverse outcomes in ELBW infants.

OBJECTIVES To examine the prevalence of early hyperglycemia and clinical outcomes among ELBW infants before (2002-2005) and after (2006-2011) the implementation of an early enhanced PN protocol and to assess the independent effects of early enhanced PN and early hyperglycemia on mortality.

DESIGN, SETTING, AND PARTICIPANTS Observational cohort study in a level III neonatal intensive care unit. Prospectively collected clinical data in the neonatal intensive care unit’s medical database, nutritional information, and blood glucose levels were merged for analysis. All ELBW infants born between January 1, 2002, and December 31, 2011, without lethal malformations and still alive at 12 hours of life were eligible for inclusion in the study.

MAIN OUTCOMES AND MEASURES Mortality was the main outcome measure. Severe hyperglycemia was defined as 2 consecutive blood glucose levels exceeding 216 mg/dL at least 3 hours apart. A multivariable logistic regression model was applied to determine the independent effects of early enhanced PN and hyperglycemia on mortality.

RESULTS In total, 343 infants were included in the study, 129 in a historical comparison group before the enhanced PN protocol and 214 in the early enhanced PN group. Baseline characteristics were similar between the study groups. After the introduction of early enhanced PN, the prevalence of severe hyperglycemia during the first week of life was higher in the early enhanced PN group (11.6% [15 of 129] vs 41.6% [89 of 214], P < .001), as was the mortality (10.9% [14 of 129] vs 24.3% [52 of 214], P = .003). When adjusting for background characteristics, treatment, and nutritional data, early severe hyperglycemia remained a strong independent risk factor for death (odds ratio, 4.68; 95% CI, 1.82-12.03), together with gestational age (odds ratio, 0.62; 95% CI, 0.49-0.79).

CONCLUSIONS AND RELEVANCE The implementation of an enhanced PN protocol was correlated with an increased prevalence of severe hyperglycemia and higher mortality. In the multivariable analysis, an enhanced PN regimen per se was not predictive of mortality, whereas early severe hyperglycemia remained strongly predictive of death. To avoid detrimental effects on outcomes in ELBW infants, the optimal composition of early PN to avoid postnatal growth failure must be carefully balanced against hyperglycemia risk.


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High blood glucose levels are common in extremely low-birth-weight (ELBW) infants (birth weight, <1000 g) during the first days of life. Hyperglycemia risk is related to increasing prematurity, growth retardation, the practice of parenteral nutrition (PN) (including lipids), high glucose infusion rates, clinical stress, and the use of corticosteroids and vasopressors. In observational studies, early hyperglycemia has been proposed as an independent risk factor for increased mortality, higher rates of retinopathy of prematurity, late-onset sepsis, intraventricular hemorrhage, necrotizing enterocolitis, and unfavorable neurodevelopmental outcomes. However, designing controlled studies to address a causal relationship between hyperglycemia and adverse outcomes in preterm infants is probably not ethically feasible, and no such studies have been conducted, to our knowledge.

Over the last decade, an enhanced PN strategy (often referred to as early aggressive PN) has been adopted for routine care in many neonatal centers. This practice has been influenced by the observation that ELBW infants are at high risk of in-hospital postnatal growth failure, which has been linked to impaired growth and poor neurodevelopmental outcomes in early childhood, although results are conflicting. However, providing optimized nutrition and concurrently avoiding hyperglycemia in extremely premature infants may represent a challenge. Guided by published recommendations, a new PN practice was implemented in the neonatal intensive care unit (NICU) at Oslo University Hospital Rikshospitalet, Oslo, Norway, toward the end of 2005. In subsequent years, we have observed in our NICU’s medical database a higher rate of insulin use, together with an increase in mortality, among ELBW infants. Consequently, we hypothesized that our nutritional practice could adversely affect hyperglycemia risk and mortality in our ELBW population. The primary aim of our study was to examine nutritional data, the prevalence of hyperglycemia, and short-term clinical outcomes in 2 periods before (2002-2005) and after (2006-2011) the implementation of an early enhanced PN protocol. Second, we aimed to assess the independent effects of early enhanced PN and early hyperglycemia on ELBW mortality over the entire 10-year period.

Methods

Infants and Data Collection

All ELBW infants at Oslo University Hospital Rikshospitalet admitted to the hospital’s level III NICU who were born between January 1, 2002, and December 31, 2011, without lethal malformations and still alive at 12 hours of life were eligible for inclusion in the study. Clinical data were prospectively collected on a daily basis in the NICU’s medical database, which is part of the Norwegian Neonatal Network. The unit’s database has been operating in its present design since 2002 and comprises detailed information on demographic and anthropometric characteristics, medical treatment, and outcome variables. Database information is kept up to date by the attending physicians. Blood glucose levels and C-reactive protein values were extracted from the hospital’s laboratory system and merged with the NICU registry data. Nutritional data were retrieved from the hospital’s medical records. The study was approved by the Privacy and Data Protection Officer at Oslo University Hospital Rikshospitalet.

Nutrition

In period 1 (2002-2005, for the historical comparison group), unit guidelines on PN in ELBW infants recommended intravenous infusion of 10% glucose for the first several days of life, with intravenous amino acids and lipids added on days 3 and 4. In period 2 (2006-2011, for the early enhanced PN group), unit guidelines recommended initiation of PN immediately after birth as soon as vascular access was established. According to this protocol, glucose infusion was initiated at a minimum rate of 8.5 g/kg/d on day 1 and was subsequently increased by 1.0 to 2.0 g/kg/d up to 15.0 g/kg/d if tolerated. The amino acids were introduced at 1.5 to 2.0 g/kg/d on the first day and the lipids at 0.5 to 1.0 g/kg/d on day 1 or 2. The amino acids and lipids were increased by 0.5 g/kg/d to a maximum of 3.5 to 4.0 g/kg/d for amino acids and 3.0 to 3.5 g/kg/d for lipids.

No changes were made regarding enteral feeding routines during the study period. Minimum enteral nutrition was initiated early (on day 1 or 2) in both periods and was increased by 10 to 20 mL/kg/d based on tolerance. The estimated nutritional content of human milk per 100 mL was 7.2 g of carbohydrates, 1.3 g of amino acids, and 4.1 g of lipids and was included in the calculation of total daily nutrition when the infants were tolerating at least 0.5 mL/h.

Hyperglycemia

Blood glucose levels were monitored 4 to 8 times a day from the first day of life and less frequently when the clinical condition was stabilized. Hyperglycemia was defined as 2 consecutive blood glucose levels within defined ranges at least 3 hours apart and was categorized as mild (151-181 mg/dL), moderate (182-216 mg/dL), or severe (>216 mg/dL) (to convert glucose level to millimoles per liter, multiply by 0.0555). Infants with hyperglycemia were classified into a single category corresponding to the highest registered level of hyperglycemia.
Furthermore, the duration of hyperglycemia within the first week of life was categorized into 3 groups denoting exposure to severe hyperglycemia for 0, 1, or 2 or more days, respectively. The definition of severe hyperglycemia corresponds to our unit's operational threshold to reduce the glucose infusion rate, initiate insulin infusion, or both. In period 2, according to the protocol, the glucose infusion rate was not reduced below a minimum of 7.2 g/kg/d (5 mg/kg/min).

Outcome Definitions
All infants were monitored until death, discharge home, or transfer to a local hospital. Verified necrotizing enterocolitis was diagnosed as stage 2 to 3 in the classification by Bell et al. Early-onset sepsis was defined as growth of bacteria in a blood culture, together with signs and symptoms compatible with infection, along with antibiotic treatment for at least 5 days or death before 5 days during the episode. When coagulase-negative staphylococci were identified, a C-reactive protein value exceeding 333 nmol/L (35 mg/L) was required for inclusion (to convert C-reactive protein value to nanomoles per liter, multiply by 9.524). Early-onset sepsis was defined as sepsis occurring before 72 hours of life and late-onset sepsis as occurring after 72 hours or longer. Intracranial pathology was diagnosed by cranial ultrasonography, which was routinely performed on days 1 and 2, 4, 7, and 14, as well as at 4 weeks and before discharge. Intraventricular hemorrhage was defined according to work by Papile et al. Cystic periventricular leukomalacia (stage 2 or higher) was diagnosed according to criteria by de Vries et al. Growth velocity was calculated as described by Patel et al.

Statistical Analysis
Group differences between periods 1 and 2 were examined using χ² test or Fisher exact test for categorical variables. Independent-samples t test was used for continuous variables.

To investigate the crude and adjusted effects of early enhanced PN on mortality, logistic regression analyses were performed. Early enhanced PN was entered into the model as a dichotomous independent variable comparing infants born in period 2 vs 1 and was always included in the statistical model. Other independent variables were based on clinical judgment and their potential confounding effect. A forward stepwise multivariable logistic regression analysis approach was also used to reduce the number of covariates in the final multivariable model. In this approach, significant variables from the univariable analysis were divided into 2 subgroups according to clinical similarity. Gestational age (GA), Clinical Risk Index for Babies (CRIB), hyperglycemia, and the use of vasopressors were significant and were included as covariates in the final model. Birth weight represented one of the study inclusion criteria and was therefore not included in the final multivariable analysis. Because severe hyperglycemia and insulin infusion during the first week of life were highly correlated, adjustments were made only for hyperglycemia.

Sensitivity analyses were performed for different scenarios to assess the extent to which an unmeasured factor could cause the main result to lose statistical significance. These scenarios were based on clinical realistic assessment and have been used in other clinical studies.

Results
Among 373 ELBW infants admitted to the NICU during the study period, 16 died before 12 hours of life, and 7 were excluded from the study because of lethal malformations. An additional 7 infants were excluded from the final analysis because of missing nutritional data.

Background characteristics, treatment, and outcome variables during the 2 periods are summarized in Table 1. Baseline characteristics in the 2 periods did not differ regarding sex, GA, CRIB, and the proportion of infants receiving antenatal corticosteroids. The most striking difference was the mortality rate, which was markedly increased in period 2. Furthermore, significant differences were observed in the incidence of necrotizing enterocolitis, the mean 5-minute Apgar score, and the proportion of infants who received surfactant in the delivery room.

Nutritional Intake and Hyperglycemia
The mean daily intake of all nutrients during the first week was significantly increased in period 2 compared with period 1 (Table 1). Enteral feeding was initiated during the first week of life for all but 6 infants. Expressed fresh breast milk from the mothers or nonpasteurized, cytomegalovirus-negative human donor milk was given to all infants who received enteral feeding in the 2 periods. Significantly more infants in period 2 attained full enteral feeding during the first week.

The proportion of infants with severe hyperglycemia above the interventional threshold was significantly higher in period 2 during the first week of life. When examining each separate day during the first week of life, we found significant differences between the 2 periods on days 0 through 4 in the intravenous glucose infusion rate and on days 0 through 6 in total carbohydrate and calorie intake, as well as in the proportion of infants with severe hyperglycemia (Figure).

PN, Hyperglycemia, and Death
The crude and adjusted effects of baseline characteristics, medical treatment, hyperglycemia, and nutrition on mortality are summarized in eTable 1 in the Supplement (univariable analysis) and in Table 2 (multivariable analysis). In the univariable analysis, early enhanced PN was associated with increased mortality (odds ratio [OR], 2.64; 95% CI, 1.39-4.98). However, in the final multivariable model, the only independent risk factors for death were early severe hyperglycemia, GA, and CRIB. Inclusion in the early enhanced PN group was not independently predictive of death in the multivariable regression model.

Sensitivity analyses for unmeasured confounding were performed using different realistic scenarios of effect (relative risk, 1.0-3.5) between an unmeasured factor and outcome.
comes. The difference in its prevalence between exposed and unexposed groups (10%-50%) showed that the lower limit of the 95% CI for severe hyperglycemia (OR, 1.82) did not reach 1.0 (eTable 2 in the Supplement). Hence, none of the tested scenarios caused the main result to lose significance.

When the multivariable analysis was repeated in 319 infants who were still alive at 7 days of life, only GA and severe hyperglycemia during the first week of life remained significant independent risk factors for death (Table 3 and eTable 3 in the Supplement). When investigating effects from the duration of severe hyperglycemia on mortality in this subgroup, the adjusted ORs of death were 6.52 (95% CI, 2.11-20.17) if exposed to severe hyperglycemia for 1 day and 12.23 (95% CI, 3.95-37.85) if exposed for 2 or more days during the first week of life (Table 4 and eTable 4 in the Supplement).

### Discussion

This observational study of a complete, unselected single-center population of 343 ELBW infants demonstrates that the introduction of an enhanced PN protocol was associated with
an increased prevalence of hyperglycemia during the first week of life, greater use of insulin, and higher mortality. When adjusting for the potential confounding factors in the multivariable regression analysis, early severe hyperglycemia remained a strong independent risk factor for death (OR, 4.68), whereas the new PN regimen did not seem to have an independent role in the risk of death. When the multivariable regression analysis was repeated for infants surviving the first week of life, early severe hyperglycemia was an even stronger risk factor for death (OR, 8.63). This finding suggests that the association between high blood glucose levels and mortality is not simply a reflection of the metabolic changes taking place in critically ill or dying infants. Furthermore, we found an association between the duration of hyperglycemia during the first week and increased mortality given survival beyond the first week of life, suggesting a dose-response relationship.

The present study adds important information to the proposed link between early hyperglycemia and mortality in ELBW infants. To our knowledge, this is the largest study on the subject in terms of the number of infants included. Furthermore, it is the first report to date to explicitly address the relationship between early enhanced PN, occurrence of hyperglycemia, and mortality by including detailed nutritional data in a multivariable regression analysis. Previously, Hays et al investigated the medical records of 93 ELBW infants and reported that a persistent glucose level exceeding 250 mg/dL during the first week of life was associated with early death and with grade 3 or 4 intraventricular hemorrhage. In a study by Kao et al, hyperglycemia exceeding 180 mg/dL in the first few days after birth was reported to increase the odds of death and sepsis in a cohort of 201 ELBW infants. In a population-based cohort that included 143 infants with GA of less than 27 weeks, Alexandrou et al demonstrated an association between hyperglycemia exceeding 8.3 mmol/L (150 mg/dL) on the first day of life and increased mortality, together with magnetic resonance imaging white matter reduction at term age.

The potential mechanisms for deleterious effects of hyperglycemia in preterm infants have been explored in experimental studies. Increased mortality has been demonstrated in hyperglycemic preterm models of baboons, lambs, and rats. In the study by Tayman et al, the histopathological and immunohistochemical evaluation of the animal brain demonstrated
Table 2. Multivariable Logistic Regression Analysis for Death Given Survival at 12 Hours of Life Among 343 Infants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early enhanced parenteral nutrition*</td>
<td>1.59 (0.69-3.64)</td>
<td>.28</td>
</tr>
<tr>
<td>Gestational age</td>
<td>0.62 (0.49-0.79)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Clinical Risk Index for Babies</td>
<td>1.11 (1.01-1.23)</td>
<td>.03</td>
</tr>
<tr>
<td>Any vasopressor use</td>
<td>1.78 (0.89-3.55)</td>
<td>.10</td>
</tr>
<tr>
<td>Hyperglycemia during the first week of life(a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>0.65 (0.16-2.66)</td>
<td>.55</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.35 (0.43-4.32)</td>
<td>.61</td>
</tr>
<tr>
<td>Severe</td>
<td>4.68 (1.82-12.03)</td>
<td>.001</td>
</tr>
</tbody>
</table>

\(a\) Hyperglycemia was defined as 2 consecutive blood glucose levels in the defined range at least 3 hours apart and was categorized as mild (151-181 mg/dL), moderate (182-216 mg/dL), or severe (>216 mg/dL). Each infant was assigned only to the highest possible category. The reference category was not having mild, moderate, or severe hyperglycemia.

Table 3. Multivariable Logistic Regression Analysis for Death Given Survival at 7 Days of Life Among 319 Infants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early enhanced parenteral nutrition*</td>
<td>1.21 (0.41-3.54)</td>
<td>.73</td>
</tr>
<tr>
<td>Gestational age</td>
<td>0.52 (0.37-0.73)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Any vasopressor use</td>
<td>1.62 (0.70-3.76)</td>
<td>.26</td>
</tr>
<tr>
<td>Hyperglycemia during the first week of life(b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>0.45 (0.05-4.31)</td>
<td>.49</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.37 (0.27-7.02)</td>
<td>.71</td>
</tr>
<tr>
<td>Severe</td>
<td>8.63 (2.41-30.95)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

\(b\) Hyperglycemia was defined as 2 consecutive blood glucose levels in the defined range at least 3 hours apart and was categorized as mild (151-181 mg/dL), moderate (182-216 mg/dL), or severe (>216 mg/dL). Each infant was assigned only to the highest possible category. The reference category was not having mild, moderate, or severe hyperglycemia.

As an observational noncontrolled study, the present investigation has several potential limitations. First, because of the high correlation between insulin therapy and severe hyperglycemia, we were unable to assess the independent effect of the use of insulin on the outcome. However, in the univariable analysis the crude effect of hyperglycemia on mortality was stronger compared with the effect of the use of insulin. Second, the correlation among early enhanced PN, hyperglycemia, and increased mortality could theoretically be biased by a population of sicker infants in period 2. Although the mean 5-minute Apgar score was significantly lower and a higher proportion of infants received surfactant in the delivery room in period 2, all other baseline characteristics that previously have demonstrated predictive effects on outcomes were similar in the 2 periods, including sex, GA, multiple birth, CRIB, and the proportion of infants receiving antenatal corticosteroids. Third, although the change in PN regimen was the most significant treatment policy alteration during the study period, unrecognized drift in other aspects of clinical practice over time may represent a potential confounder within an observational study design. However, given the large sample size and the prospective collection of detailed treatment and outcome data, we believe that potentially confounding treatment factors were well adjusted for in the multivariable analysis. Furthermore, based on sensitivity analyses, we found it unlikely that any unmeasured confounder could significantly alter these findings.

There is no consensus regarding the definition of hyperglycemia in ELBW infants. In the observational studies\(^2\),\(^3\),\(^6\),\(^8\),\(^10\),\(^11\) mentioned earlier, the definition of hyperglycemia varied between 150 and 250 mg/dL. In the present study, hyperglycemia was classified as mild, moderate, or severe for pragmatic reasons, with severe hyperglycemia corresponding to our NICU’s interventional threshold. Only severe hyperglycemia significantly increased the OR for mortality in the multivariable analysis. A too tight regimen for glycemic control may increase the risk of potentially deleterious hypoglycemic episodes. In a recent randomized clinical trial of 88 hyperglycemic infants with GA of less than 30 weeks or birth weight of less than 1500 g, tight glycemic...
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control with insulin (target range, 4-6 mmol/L) was compared with standard treatment (target range, 8-10 mmol/L). The authors reported increased weight gain and head growth in the tight glycemic control group but at the expense of reduced linear growth and increased risk of hypoglycemia. Therefore, the safe target range for blood glucose levels in ELBW infants remains a subject for further research.

Along with aiming to enhance the survival of ELBW infants, attempts to optimize early PN to promote the best postnatal growth and development may have increased the hyperglycemia risk in the NICU. In the present study, the prevalence of early hyperglycemia was high in period 2, although similar data have been reported by others. We speculate that a higher prevalence of hyperglycemia after the implementation of an enhanced PN protocol may in part be explained by the use of more concentrated glucose solutions, increasing the risk of intermittent iatrogenic excessive intravenous glucose delivery. Based on the insights gained in the present study, we advocate strict control of the glucose infusion rate during early PN, including rapid reduction to a rate of 4 to 6 mg/kg/min once blood glucose levels are elevated. Furthermore, recent data have suggested that higher early protein infusion rates in the range of 3.5 to 4.0 g/kg/d may reduce the prevalence of hyperglycemia, probably by stimulating endogenous insulin production.

The present study documented a significantly lower amino acid supply during both periods, indicating potential for further improvement of our nutritional practice. The role of exogenous insulin in the prevention and treatment of hyperglycemia in preterm infants remains controversial. Until further data are available, we believe that the use of insulin should be restricted to refractory cases of hyperglycemia.

Conclusions

In this observational study of a complete, unselected single-center ELBW population, the introduction of an early enhanced PN protocol was associated with an increased incidence of early hyperglycemia, greater use of insulin, and higher mortality. When adjusting for relevant covariates, the new PN regimen was not independently associated with mortality. However, early severe hyperglycemia remained a strong independent risk factor for death. To avoid detrimental effects on outcomes in ELBW infants, the optimal composition of early PN to avoid postnatal growth failure must be carefully balanced against hyperglycemia risk.


