ARTICLE

Hyperglycemia Is a Risk Factor for Early Death and Morbidity in Extremely Low Birth-Weight Infants

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ABSTRACT

OBJECTIVES. The objectives of this study were to determine the prevalence of hyperglycemia in extremely low birth-weight infants and to determine whether hyperglycemia increases the risk of early adverse outcomes (death or intraventricular hemorrhage of grade 3 or 4) and/or affects the length of hospital stay among survivors without intraventricular hemorrhage.

METHODS. The charts of all extremely low birth-weight infants (n = 93) admitted to Texas Children’s Hospital (Houston, TX) during 2001 were reviewed. The highest daily blood glucose concentrations, highest dopamine infusion rates, highest daily percentage of inspired oxygen, and mean blood sodium concentrations were averaged over the first week of life or before death or occurrence of grade 3 or 4 intraventricular hemorrhage. Among survivors without severe intraventricular hemorrhage, the time ratio for blood glucose concentrations of >150 mg/dL was calculated.

RESULTS. More than 50% of the infants had persistent blood glucose concentrations of >150 mg/dL during their first week of life. Early adverse outcomes were associated with the average highest daily blood glucose concentration through interaction with the Clinical Risk Index for Babies score and with the average highest daily percentage of inspired oxygen. The length of hospital stay was associated with the time ratio for blood glucose concentrations of >150 mg/dL through interaction with birth weight and the average highest daily percentage of inspired oxygen.

CONCLUSION. These data confirm the high prevalence of hyperglycemia among parenterally fed, extremely low birth-weight infants and show that high blood glucose concentrations increase the risk of early death and grade 3 or 4 intraventricular hemorrhage and the length of hospital stay among survivors without intraventricular hemorrhage, which suggests that prevention and treatment of hyperglycemia may improve the outcomes of extremely low birth-weight infants.
Hyperglycemia is associated with increased mortality and morbidity rates among non-diabetic adults admitted to ICUs for treatment of myocardial infarction, stroke, or trauma and among adults admitted to the hospital. Similar findings were reported recently for PICU patients. Moreover, a historical comparison study in an ICU and a randomized, controlled trial in a surgical ICU, conducted with adults, showed beneficial effects of insulin therapy and well-controlled blood glucose concentrations on both mortality and morbidity rates. Several of those studies indicated that hyperglycemia was an independent risk factor for both death and morbidity for adult and pediatric patients. In addition, Ertl et al reported an increased prevalence of retinopathy of prematurity among hyperglycemic (blood glucose concentrations of >155 mg/dL) very low birth-weight infants.

Numerous studies have reported a high prevalence of hyperglycemia in extremely low birth weight (ELBW) infants, particularly during their first week of life. Hyperglycemia is indirectly related to birth weight (eg, Louik et al reported a 18 times greater prevalence in infants with birth weights of <1000 g, compared with >2000 g) and gestational age and is directly related to illness (eg, septicemia), to treatment with corticosteroids, and to intravenous glucose infusions given at rates exceeding normal infant glucose turnover rates (~6 mg/kg per minute). Hyperglycemia in very sick patients is most likely an effect of stress and thus increased levels of catecholamines, which are known to stimulate glucose metabolism. In this regard, very premature infants are not different from older, critically ill patients. However, the glucose intolerance observed in otherwise healthy, premature infants receiving glucose infusions at rates exceeding their normal glucose turnover rate is specifically related to their immaturity and might be a result of absolute or relative insulin insufficiency, hepatic and peripheral insulin resistance, inadequate responsiveness to insulin and/or glucose, and the small mass of insulin-dependent tissue (primarily muscle and fat).

Hyperglycemia is frequently accompanied by urinary loss of glucose and osmotic diuresis, with its risk of dehydration. In addition, hyperglycemia leads to hyperosmolarity and osmotic shifts, which increase the risk of cerebral bleeding. However, ELBW infants (birth weights of <1000 g) are already at risk of cerebral bleeding, particularly during their first week of life, as a result of immature blood vessels in the germinal matrix and not fully developed autoregulation of cerebral blood pressure. Because the brain is the principal glucose consumer, accounting for 90% of glucose utilization in newborn infants, a large cerebral bleeding will disturb brain metabolism and reduces its glucose consumption, leading to hyperglycemia. Therefore, cerebral bleeding can be the cause or the consequence of hyperglycemia.

To the best of our knowledge, there are no published reports addressing the relationship between hyperglycemia and death or neurologic morbidities among ELBW infants. The aim of this study was to assess the association of blood glucose concentrations with the occurrence of severe intraventricular hemorrhage (IVH) (grade 3 or 4) or death in ELBW infants during their first week of life, as well as the length of stay (LOS) in the hospital. We hypothesized that hyperglycemia during the first week of life (1) has a high prevalence among ELBW infants receiving parenteral nutrition, (2) is a risk factor for early adverse outcomes by 10 days of life (death or grade 3 or 4 IVH), and (3) is associated with increased LOS among survivors without IVH.

METHODS

Review Board Approval

This protocol was approved by the institutional review board for Baylor College of Medicine and affiliated hospitals and by the advisory board for the General Clinical Research Center at Texas Children’s Hospital (Houston, TX). The institutional review board granted a waiver of consent requirements for this retrospective chart review.

Population

The charts of all ELBW infants (ie, with birth weights of <1000 g) who were admitted to the level 3 nursery at Texas Children’s Hospital between January 1, 2001, and December 31, 2001, were reviewed. During that period, 93 ELBW infants were admitted. Of those 93 infants, 11 infants were excluded, 1 because of complex congenital heart disease (the infant received different fluid management, compared with the remaining infants, and received prostaglandin E1 treatment), 4 because of death on the first day of life, 4 because of the occurrence of IVH on the first day of life, and 2 because of missing flow-sheets. None of the infants underwent surgery during the first 7 days of life.

Data Collection

From the charts of the 82 remaining infants (birth weight: 760 ± 158 g; gestational age: 25.4 ± 1.9 weeks), we collected demographic characteristics, including gestational age (best obstetric record), birth weight, intrauterine growth, prenatal steroid exposure, and Clinical Risk Index for Babies (CRIB) score. We registered the lowest and highest blood glucose concentrations, the mean blood sodium concentration, the highest dopamine infusion rate, and the highest percentage of inspired oxygen daily during the first 7 days of life. The charts did not have any information regarding the method used to measure blood glucose concentrations; however, according to the routines in the nursery, we can assume that the measurements were performed by
the central laboratory with whole blood, using the glucose oxidase method.

As pointed out above, significant cerebral bleeding (grade 3 or 4 IVH, according to the system described by Papile et al\textsuperscript{33}) can be a cause of hyperglycemia. Therefore, we also reviewed the head ultrasound scan reports. These scans were not performed on a daily basis; therefore, the bleeding could have occurred any day before the scan. To date the bleeding, all hematocrit values from birth to the day on which IVH of grade 3 or 4 was noted on the scan were reviewed. A decrease of \( \geq 10 \) percentage points between 2 consecutive values in \(<24\) hours was considered to indicate that the IVH occurred on that day, provided that no other event reported in the chart could explain such a decrease. To assess the validity of a 10-percentage point cutoff value, we reviewed the charts of all infants with hematocrit decreases of \( \geq 10 \) percentage points who did not have a history of grade 3 or 4 IVH. For all of those patients, an explanation for the decrease was found (intestinal perforation with bloody stool, hemorrhage, dilution attributable to administration of a large volume of albumin, or unusually large blood volume drawn because of the severity of illness). In addition, the LOS and the postmenstrual age at discharge (PMAD) were determined.

### Outcome Definition

An early adverse event was defined as death or the occurrence of grade 3 or 4 IVH before day 10 of life. It is well known that the greatest risk for IVH is within the first 2 weeks of life. No grade 3 or 4 IVH occurred after day 10 in our cohort. A nonadverse outcome was defined as being alive on day 10 of life without grade 3 or 4 IVH.

### Calculations

The prevalence of hyperglycemia on each day of the first week was calculated by using thresholds of 150, 200, 250, 300, and 500 mg/dL. For each infant, we calculated the average (1) highest daily blood glucose concentration, (2) highest daily dopamine infusion rate, (3) highest daily percentage of inspired oxygen, and (4) highest daily blood sodium concentration during the first 7 days or before death or the occurrence of grade 3 or 4 IVH (whichever came first).

The analysis of the effect of glucose concentrations on LOS and PMAD used the time ratio for glucose concentrations of \( >150\) mg/dL. This ratio was calculated as the number of daily lowest blood glucose concentrations of \( >150\) mg/dL divided by the total number of days for which a glucose value was available during the first 7 days of life. Seventy-seven percent of the cases of grade 3 or 4 IVH occurred during the first 1 to 3 days of life, potentially resulting in persistent hyperglycemia (attributable to large areas of metabolically inactive tissue, leading to reduced glucose uptake) during the remaining days of the first week (the period considered in the calculations of the time ratio). Therefore, to avoid potential bias, the time ratio for blood glucose concentrations of \( >150\) mg/dL was calculated only for infants who survived to discharge without grade 3 or 4 IVH.

### Statistical Analyses

Statistical analyses were conducted with SPSS 13.0 (SPSS, Chicago, IL) and Minitab 13.31 (Minitab, State College, PA). Multivariate logistic regression analysis was used to assess the risk of death or grade 3 or 4 IVH, whereas multivariate linear regression analysis was used to evaluate the effects on LOS and PMAD. Univariate analyses were performed by using \( P < .2 \), to select a subset of variables to be controlled. These variables were then introduced in a multivariate regression analysis. Because the role of glucose as a risk factor for adverse outcomes was the major focus of this study, we tested for interactions between glucose and each other variable. A manual backward-elimination approach was used to eliminate nonsignificant interactions. For early adverse outcomes, the clinical relevance of significant interactions was assessed by using \( 2 \times 2 \) tables. The cutoff values for variables involved in the interaction with glucose concentrations were defined as the best values predicting an early adverse outcome with a receiver operating characteristic curve. There is no reason to believe that vulnerable ELBW infants would tolerate higher blood glucose concentrations than older children and adults. Therefore, the cutoff value for glucose concentrations was set at 150 mg/dL, because this value is used commonly for older children and adults. For continuous outcomes (LOS and PMAD), the median for each variable included in the interaction term was used as the cutoff value.

### RESULTS

#### Prevalence of Hyperglycemia

Blood glucose measurements were available for 80 of 82 infants on days 1 and 2, for 70 of 82 infants on day 3, for 63 of 82 infants on day 4, for 58 of 82 infants on day 5, for 52 of 82 infants on day 6, and for 44 of 82 infants on day 7. To avoid potential overestimation of the prevalence of hyperglycemia, we assumed that, for infants for whom no blood glucose measurements were available, blood glucose measurements had been discontinued because they were \(<150\) mg/dL. With these conservative calculations, the prevalence of hyperglycemia from the second day to seventh day of life was 32% with a threshold of 250 mg/dL and 57% with a threshold of 150 mg/dL. Forty-two percent of the ELBW infants had blood glucose concentrations that were consistently \( >150\) mg/dL from the second day to seventh day of life (ie, no values were \(<150\) mg/dL during this period); for 25% and 16% of the infants, blood glucose concentra-
tions were consistently >200 mg/dL and >250 mg/dL, respectively (Tables 1 and 2).

**Impact on Early Adverse Outcomes**

On the basis of the results from the univariate logistic regression analyses (Table 3), the following variables were introduced in the multivariate analysis: average highest daily blood glucose value, gestational age, birth weight, gender, CRIB score, prenatal steroid exposure, average highest daily dopamine infusion rate, average highest daily percentage of inspired oxygen, and interaction between the average highest daily blood glucose value and each of these variables. Interactions between the average highest daily blood glucose concentration and the CRIB score and between the average highest daily blood glucose concentration and the average highest daily percentage of inspired oxygen remained significant in the multivariate model (Table 3).

To illustrate the interactions, receiver operating characteristic curve analyses were used to define thresholds for variables involved in the interaction with glucose concentrations. These thresholds were 50% for the average highest daily percentage of inspired oxygen and 8 for the CRIB score. The cutoff value for the average highest daily blood glucose concentration was set at 150 mg/dL, because this value is used commonly to define hyperglycemia in older children and adults. With this glucose threshold, sensitivity and specificity for predicting an early adverse outcome were 91% and 25%, respectively. When the highest daily percentage of inspired oxygen was >50%, the risk of an adverse outcome was 57% when the glucose concentration was >150 mg/dL, compared with 33% when the average highest daily blood glucose concentration was <150 mg/dL (Fig 1). When the percentage of inspired oxygen was <50%, the risks of an adverse outcome were 11% and 7%, when the blood glucose concentration was >150 mg/dL and <150 mg/dL, respectively (Fig 1). When the CRIB score was >8, the risk of an adverse outcome was 43% when the glucose concentration was >150 mg/dL, compared with 20% when the glucose concentration was <150 mg/dL (Fig 1). When the CRIB score was <8, the risks of an adverse outcome were 12% and 8% when the blood glucose concentration was >150 mg/dL and <150 mg/dL, respectively (Fig 1).

**Factors Affecting LOS Among Survivors Without IVH**

Forty-eight ELBW infants (birth weight: 785 ± 163 g; gestational age: 25.8 ± 2.0 weeks) survived until discharge without grade 3 or 4 IVH. After controlling for the significant variables in the univariate analyses of potential factors influencing LOS, interactions between the time ratio for blood glucose concentrations of >150 mg/dL and the average highest daily percentage of inspired oxygen and between the time ratio for blood glucose concentrations of >150 mg/dL and birth weight were correlated significantly with LOS, whereas the average highest daily blood glucose concentration no longer affected LOS significantly (Table 4).

In addition, after controlling for significant variables in the univariate analysis of PMAD, the interaction between the time ratio for glucose concentrations of >150 mg/dL and the average highest daily percentage of inspired oxygen was significantly correlated with PMAD. However, the correlation between the average highest daily blood glucose concentration by itself or through any interaction and PMAD did not remain significant (Table 5).

To analyze more thoroughly the overall effects of the time ratio for blood glucose concentrations of >150 mg/dL on LOS and PMAD, in relation to the highest daily percentage of inspired oxygen and birth weight, 2 × 2 tables were constructed by using the median for the time ratio for blood glucose concentrations of >150 mg/dL (0.33), the median for the average highest daily percentage of inspired oxygen (40%), and the median for birth weight (800 g). For the group of survivors to discharge, these analyses demonstrated a large effect of the time ratio for blood glucose concentrations of >150 mg/dL when the average daily percentage of inspired oxygen was >40% (182 vs 119 days, ie, a difference of 63 days) (Fig 2), whereas there was no effect when the average highest daily percentage of inspired oxygen was <40%. With regard to birth weight, the time ratio for glucose concentrations of >150 mg/dL affected LOS regardless of birth weight, although the effect was greater when the birth weight was <800 g (131 vs 90 days, ie, a difference of 41 days), compared with >800 g (157 vs 134 days, ie, a difference of 23 days) (Fig 2). The effect of the time ratio for glucose concentrations of >150 mg/dL on PMAD was also observed only when the average daily percentage of inspired oxygen was >40%.

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**Table 1: Prevalence of Infants With All Blood Glucose Values Above the Threshold (Calculated With the Lowest Daily Value)**

<table>
<thead>
<tr>
<th>Threshold, mg/dL</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
</tr>
</thead>
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<tr>
<td>150</td>
<td>16</td>
<td>54</td>
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<td>45</td>
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<td>30</td>
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<td>32</td>
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<td>17</td>
<td>16</td>
<td>13</td>
<td>12</td>
</tr>
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<td>9</td>
<td>7</td>
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<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
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**References:**


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highest daily percentage of inspired oxygen was >40% (Fig 3).

**DISCUSSION**

Our results confirm the previously reported high prevalence of hyperglycemia among parenterally fed ELBW infants. Between day 2 and day 7 of life, nearly 60% of our infants had blood glucose concentrations of >150 mg/dL and ~30% had concentration of >250 mg/dL; for ~50% of the infants, blood glucose concentrations were persistently >150 mg/dL during this period. Furthermore, already during the first day of life, 25% of our cohort had ≥1 value of >250 mg/dL and 50% had ≥1 value of >150 mg/dL. For ELBW infants, the inability to match glucose disposal to the glucose inflow frequently results in hyperglycemia when the glucose infusion rate exceeds the normal infant glucose turnover rate of ~6 mg/kg per minute.36–42 In our study, the glucose infusion rate was 6.0 ± 1.2 mg/kg per minute on the first day of life and then was increased in a stepwise manner to average 9.8 ± 2.0 mg/kg per minute on the seventh day of life. Although they were not extremely high, these infusion rates exceeded the normal infant glucose turnover rate after the first day of life, which might have contributed, at least in part, to the observed high prevalence of hyperglycemia.

Although there is no reason to believe that vulnerable ELBW infants would tolerate high blood glucose concentrations better than older children and adults, there is no consensus regarding the threshold of blood glucose concentrations defining hyperglycemia in preterm infants,43 mainly because of a lack of data on the impact of blood glucose concentrations on short- and long-term outcomes for this population. Therefore, the present retrospective study was conducted to explore potential associations between blood glucose concentrations and early adverse outcomes, defined as grade 3 or 4 IVH or

<table>
<thead>
<tr>
<th>Threshold, mg/dL</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
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<td>1</td>
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**TABLE 2** Prevalence of Infants With at Least 1 Value Above the Threshold (Calculated With the Highest Daily Value)

**TABLE 3** Characteristics of Infants With Early Adverse and Nonadverse Outcomes and Logistic-Regression Analysis for Early Adverse Outcomes

AvHglc indicates average highest daily blood glucose concentration; AvHOxygen, average highest daily percentage of inspired oxygen; AvHDopa, average highest daily dopamine infusion rate; AvNa, average daily blood sodium concentration; NA, not applicable; SGA, small for gestational age.
death, by using logistic regression analysis with blood glucose concentration as a continuous variable. We demonstrated that blood glucose concentrations in interaction with the CRIB score and with the average highest daily percentage of inspired oxygen had significant effects on early adverse outcomes among ELBW infants. The prognosis worsened for ELBW infants with an average daily glucose concentration of \( \geq 150 \) mg/dL, regardless of oxygen requirement and CRIB score (Table 3), which indicates that blood glucose concentration is a significant factor affecting the outcome of ELBW infants; this emphasizes the importance of prevention and treatment strategies aimed at normoglycemia.

Because there is no reason to believe that ELBW infants would be more tolerant to high blood glucose concentrations than older children and adults, for whom hyperglycemia is commonly defined as a blood glucose concentration of \( >150 \) mg/dL, it seems appropriate to use this cutoff value also in the neonatal period. The

### TABLE 4 Linear-Regression Analysis for LOS

<table>
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<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariate</th>
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</thead>
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<td>AvHglc</td>
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</tr>
<tr>
<td>TR&gt;150</td>
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<td>0.57</td>
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<tr>
<td>Gestational age</td>
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<tr>
<td>Birth weight</td>
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<td>0.057</td>
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<tr>
<td>CRIB score</td>
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<tr>
<td>Prenatal steroids</td>
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<td>AvHOxygen</td>
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<td>AvHDopa</td>
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<tr>
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<td>NA</td>
</tr>
<tr>
<td>TR&gt;150-AvHOxygen</td>
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<td>NA</td>
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</table>

AvHglc indicates average highest daily blood glucose concentration; TR>150, time ratio for blood glucose levels of \( >150 \) mg/dL; AvHOxygen, average highest daily percentage of inspired oxygen; AvHDopa, average highest daily dopamine infusion rate; AvNa, average daily mean blood sodium concentration; \( \beta \), linear regression coefficient; NA, not applicable.

### TABLE 5 Linear-Regression Analysis for PMAD

<table>
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<td>AvHglc</td>
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<tr>
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<td>AvNa</td>
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<tr>
<td>TR&gt;150-AvHOxygen interaction</td>
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<td>NA</td>
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</table>

AvHglc indicates average highest daily blood glucose concentration; TR>150, time ratio for blood glucose levels of \( >150 \) mg/dL; AvHOxygen, average highest daily percentage of inspired oxygen; AvHDopa, average highest daily dopamine infusion rate; AvNa, average daily mean blood sodium concentration; \( \beta \), linear regression coefficient; NA, not applicable.

![Time ratio of glucose concentration](image)

FIGURE 2 Effects of average highest daily percentage of inspired oxygen and birth weight on LOS with time ratios for glucose concentrations of \( >150 \) mg/dL below or above the median value of 0.33.
prevalence of blood glucose concentrations of >150 mg/dL was high in our cohort (based on lowest or highest daily value). Because sustained blood glucose concentrations above this value are likely more detrimental for outcomes than are occasional blood glucose concentrations of >150 mg/dL, we decided to use a time ratio for glucose concentrations of >150 mg/dL, calculated as the number of days with a lowest blood glucose value of >150 mg/dL divided by the total number of days on which blood glucose concentrations were obtained during the first week of life. This parameter was used in the analyses of the impact of blood glucose concentrations on the LOS and PMAD for infants surviving without severe IVH (grade 3 or 4). The time ratio for blood glucose concentrations of >150 mg/dL had significant effects on LOS and PMAD through interactions with the average highest daily percentage of inspired oxygen and birth weight, respectively (Fig 2). A time ratio of >0.33 (the median used as a threshold in the analysis) increased LOS and PMAD regardless of birth weight and oxygen requirement, but the effect was greater for the smallest infants and those with the greatest oxygen requirements (Fig 3). The average highest daily blood glucose value did not remain a significant determinant of LOS or PMAD when other factors were controlled for, however, which indicates that prolonged periods with blood glucose concentrations of >150 mg/dL had greater effects on these parameters than did isolated very high blood glucose values. Although the present study does not have the strength of a randomized trial, our results suggest that a blood glucose concentration of 150 mg/dL might be an appropriate interventional threshold to be used in defining nutritional and treatment strategies to improve early outcomes and to reduce the LOS.

We did not assess the risk of adverse outcomes associated with being small for gestational age, because all infants who were small for gestational age were alive without severe IVH on day 10 of life. We are aware that the CRIB score, which is primarily an indicator of mortality risk, is not validated for ELBW infants, but there is no other risk score valid for ELBW infants that can be applied readily in a retrospective study. It is noteworthy that the CRIB score was significantly higher for group 1 (infants with grade 3 or 4 IVH or early death) than for group 2. As expected, the CRIB score was not a significant predictor of LOS or PMAD, whereas the percentage of inspired oxygen and the time ratio for glucose concentrations of >150 mg/dL had significant effects on LOS and PMAD, although only values representing the first week of life were included in the analyses. With regard to the percentage of inspired oxygen, we speculate that its impact on LOS was related to bronchopulmonary dysplasia, because infants with severe IVH and an infant with a complex heart malformation were excluded from the analyses.

CONCLUSIONS

Hyperglycemia occurs very frequently among parenterally fed ELBW infants. We demonstrated that blood glucose concentrations had significant effects on both early death and the occurrence of severe IVH. Furthermore, the longer ELBW infants had blood glucose concentrations of >150 mg/dL during their first week of life, the longer they stayed in the hospital and the greater the PMAD. It is well known that the incidence of bronchopulmonary dysplasia increases with decreasing birth weight and that reduced growth rate and increased oxygen requirements increase the LOS. We demonstrated that the time ratio for glucose concentrations of >150 mg/dL amplified the effects of birth weight on LOS. We speculate that prolonged hyperglycemia might have a deleterious effect on lung tissue, perhaps by inducing hyperosmolarity or triggering oxidative stress. Our results contribute to the growing body of data demonstrating that high blood glucose concentrations have detrimental effects on the outcomes of not only critically ill pediatric, adult, or elderly patients but also ELBW infants. The potential benefits of nutritional strategies and insulin treatment in controlling blood glucose concentrations in ELBW infants need to be addressed.

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