Long Duration of Hyperglycemia in the First 96 Hours of Life Is Associated with Severe Intraventricular Hemorrhage in Preterm Infants

Adi Auerbach, MD[1,*], Smadar Eventov-Friedman, MD, PhD[2,*], Ilan Arad, MD[2], Ofra Peleg, MD[2], Tali Bdolah-Abram, MSc[3], Benjamin Bar-Oz, MD[2], and David Haim Zangen, MD[1]

Objective To assess the association between severe intraventricular hemorrhage (IVH) and blood glucose variables during the first 96 hours of life in preterm infants.

Study design Preterm infants with IVH grade 3-4 (n = 70) were compared with matched infants of similar gestational age and birth weight, but with no IVH (n = 108). Studied variables included the frequency and duration of hyper/hypoglycemic (>6.9/<3.3 mmol/L, respectively) events, the extreme slope of an event evolution, the maximal glucose value observed, and the "hyper/hypoglycemic index" representing a weighted average of the hyper/hypoglycemic amplitude.

Results The IVH group had significantly more hyperglycemic events (2.9 ± 1.7 vs 2.4 ± 1.8 events, $P < .05$) with longer duration (22.2 ± 14.2 vs 14.1 ± 12.5 hours, $P < .001$) and a higher hyperglycemic index (1.0±0.9 vs 1.4±1.0, $P = .003$) compared with the non-IVH controls. Respiratory distress syndrome, hypotension, and thrombocytopenia increased the adjusted OR for IVH. Hypoglycemia was not independently associated with IVH. Conversely, the increase in hyperglycemic duration was most prominently increasing the aOR for severe IVH (OR = 10.33, 95% CI = 10.0-10.6, $P = .033$).

Conclusion Longer duration of hyperglycemia in the first 96 hours of life was most strongly associated with severe IVH in preterm infants. Consequently, interventional studies to determine the selective effect of continuous control of long-lasting hyperglycemia by appropriate and timed insulin treatment on the incidence of severe IVH are warranted. *(J Pediatr 2013;163:388-93)*.

Intraventricular hemorrhage (IVH), occurring usually within the first 4 postnatal days, is a major cause of morbidity and mortality in preterm infants.[1-3] Its pathophysiology involves bleeding from fragile blood vessels in the germinal matrix, which respond poorly to frequent changes in blood flow.[1,4,5] Several risk factors, such as low gestational age and birth weight, perinatal stress, low Apgar score, and postnatal complications (eg, respiratory distress syndrome (RDS) or blood pressure instability),[6] have been associated with IVH. Less studied is the association between the frequent alterations in blood glucose levels in preterm infants[7-12] and the resultant changes in cerebral blood flow and osmolarity,[7] which may challenge the fragility of blood vessels and contribute to the development of IVH.

Hyperglycemia has lately been associated with increased mortality and morbidity rates, and insulin therapy and well-controlled blood glucose levels were found to be beneficial in adults and children in intensive care units.[13-16] In extremely low birth weight infants (birth weight <1000 grams), high blood glucose concentration was associated with increased risk for IVH grade 3-4 and mortality.[17] However, no causal relationship has been proven so far between the hyperglycemic amplitude and a detrimental outcome in interventional studies.[18] Furthermore, recent attempts to treat all extremely low birth weight infants with continuous insulin infusion early in life (Neonatal Insulin Therapy in Europe Trial) failed to have a clinical benefit but, rather, increased the incidence of hypoglycemic episodes and mortality rate at 28 days.[19]

In this study, we aimed to identify which of the specific glucose homeostatic alterations (not necessarily the amplitude) may predict the occurrence of severe IVH (grade 3 or 4) and consequently be used to monitor an interventional protocol aiming to decrease the incidence of IVH.

Methods

The data for this observational study were extracted from the Hadassah University Hospital's neonatal intensive care unit (NICU) admission records of all neonates whose birth weights were below 2000 g during 5 consecutive years

IVH	Intraventricular hemorrhage
NICU	Neonatal intensive care unit
PDA	Patent ductus arteriosus
RDS	Respiratory distress syndrome
US	Ultrasound

From the [1]Division of Pediatric Endocrinology, Department of Pediatrics, [2]Department of Neonatology, and [3]School of Public Health, Hadassah Hebrew University Medical Center, Jerusalem, Israel

*Contributed equally.

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(n = 907). The IVH study group included all neonates (n = 70) diagnosed with severe (grade 3 or 4) IVH by at least 2 cranial ultrasound (US) studies performed routinely within the first 3 days of life and subsequently between 5 and 10 days of life (subsequent US studies were performed as clinically indicated). IVH grading was determined independently by a radiologist and at least 2 neonatologists according to the Papile criteria.[3] Grade 3 IVH was characterized by germinal matrix hemorrhage with ventricular dilatation (clot fills more than 50% of the ventricles), and in grade 4 IVH the hemorrhage was also intraparenchymal. The control non-IVH group (n = 108) consisted of neonates (1 or 2 according to availability) delivered immediately before or after a study group case with similar gestational age (±10 days) and birth weight (±150 g) but with no IVH (of any grade) by the routine US studies. One neonate from the IVH group and 5 from the control group were excluded from the study because of missing data.

Based on previous studies examining risk factors for IVH in preterm infants,[1,6] we studied the following background characteristics: gestational age, birth weight, multiple gestation, primiparity, etiology of early delivery, type of delivery, intrauterine growth retardation, pregnancy complications (preeclamsia, chrioamnionitis, bleeding) Apgar scores, first hematocrit, antenatal corticosteroids exposure, the presence of thrombocytopenia (platelets count <100 000), RDS, hypotension requiring therapy (dopamine or dobutamine), early onset sepsis (positive blood culture during the first 3 days of life), clinically significant patent ductus arteriosus (PDA), necrotizing enterocolitis, skin bruising, hyperbilirubinemia, and neonatal indomethacin treatment administered for closure of PDA.

Glucose Homeostasis Calculations and Variables

Soon after birth, continuous glucose infusion was administered to all preterm infants at a rate of 4-7 mg/kg/min to match basal requirements and to prevent hypoglycemia. Routine (NICU protocol) bedside glucometer monitoring was performed 8 times daily in all infants during the initial days of life. Higher blood glucose monitoring frequency (12-24 times daily) was performed when clinical stability or blood glucose levels were deranged. Hospital laboratory confirmation of glucometer readings was done at least once daily. Glucose values for the first 4 days of life were collected from the NICU standard records. Three infants in the control group missed 1-4 hours and 11 infants in the study group lacked 6-58 hours because of early death.

Hyperglycemia and hypoglycemia were defined as glucose levels >6.9 mmol/L (>125 mg/dL) and <3.3 mmol/L (<60 mg/dL), respectively. Insulin was used whenever blood glucose levels were higher than 11.1 mmol/L (200 mg/dL) in 2-3 consecutive measurements.

The glucose homeostasis variables studied for each neonate included: (1) the number of hyperglycemic and hypoglycemic events; (2) the duration of these events; (3) the percentage of time the neonates were hypoglycemic or hyperglycemic during the 4-day period or relative to the time of data collection for this infant (the "relative duration"); (4) the maximal slope of an event evolution being the largest quotient calculated from the change in the glucose levels divided by the time of its evolution; (5) the maximal glucose value; and (6) the "hyper/hypoglycemic index," which was calculated by multiplying the amplitude size of each abnormal glucose reading by its time duration. The cumulative sum of those products divided by total hyperglycemic or hypoglycemic duration per neonate gives a general index of glucose homeostasis representing glucose stability or instability for each infant.

In order to correlate between the occurrence of hyperglycemic-associated IVH and the general illness severity of preterm infants, we created a semi-quantitative severity index score (0-5) based on death (5), days of ventilation (none = 0, up to 7 days = 1, more than 7 days = 2), bronchopulmonary dysplasia (O_2 requirement at 36 weeks corrected gestational age, no = 0, yes = 1), need for dopamine treatment (no = 0, yes = 1), and day of enteral feeds commencement (up to 4 days = 0, more than 4 days = 1). Then we correlated the final severity score with the different hypo/hyperglycemic variables.

Statistical Analyses

Independent sample *t* test was used for comparison of quantitative variables between the IVH and control groups. The Pearson χ^2 test was applied for testing the association between the study groups and qualitative variables. The variables found to be significantly ($P < .05$) associated with the dependent variable (IVH or control) in the univariate analysis were entered in a stepwise manner into a multivariate logistic regression model. The simultaneous effect of different variables and their calculated aOR and 95% CI were then assessed. All tests applied were 2-tailed, and a *P* value of 5% was considered statistically significant. Kruskal–Wallis test (nonparametric ANOVA for small subgroups with abnormal distribution) was used for correlating the severity score to glycemic variables.

Results

The birth weights of the IVH and control groups were similar by multivariate analysis (Table I). Lower gestational age, lower Apgar score at 5 minutes, and the occurrences of RDS, mechanical ventilation, pneumothorax, thrombocytopenia, hypotension, early sepsis, and bruising were found to be significantly associated with the occurrence of severe IVH. Antenatal maternal corticosteroid therapy and neonatal indomethacin treatment were more common in the control group and appeared to be protective against IVH. No statistically significant association with IVH was found for multiple gestation, primiparity, type of delivery, first hematocrit level or the presence of chorioamnionitits, preeclampsia, PDA, necrotizing enterocolitis, or hyperbilirubinemia.

When the statistically significant (IVH associated) background variables ($P < .05$) were introduced into a multivariate analysis, only RDS, thrombocytopenia, and