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

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Abbreviations and acronyms: Extremely preterm (EPT)

Abstract

Objectives: To explore the prevalence of hyperglycemia and the associations between nutritional intakes, hyperglycemia, insulin treatment and mortality in extremely preterm (EPT) infants.

Study design: Prospectively collected data from the Extremely Preterm Infants in Sweden Study (EXPRESS) was used in this study with 580 infants born <27 gestational weeks during 2004-2007 included. 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 two 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 doubled 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 EPT infants throughout the first postnatal month. Glucose infusions seem to have only a minimal impact on glucose concentrations. Insulin treatment is associated with lower mortality in infants with hyperglycemia. Current practices of hyperglycemia treatment in EPT infants should be reevaluated and assessed in randomized controlled clinical trials.

Introduction

Extremely preterm (EPT) infants are prone to disturbances in the glucose homeostasis. It has been shown that during the first postnatal week, about a third of very low birth weight infants (< 1500 g) have glucose concentrations > 180 mg/dL (10 mmol/L) (1-3). Most of the studies in the field do not focus on later weeks. However, recent studies suggest that these preterm infants may experience frequent hyperglycemia episodes nearing the time of discharge (4,5).

There is no established definition of hyperglycemia in EPT 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 various morbidity and mortality outcomes (8-15).

This study aims to describe the trends in plasma glucose concentrations in EPT 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 would account for most of the variability in glucose concentrations, and that insulin treatment would be associated with lower mortality in hyperglycemic infants.

Patients and Methods

Study population

The present study 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.

Data collection

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. In case of a single glucose value 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 by Nutrium AB, Umeå, Sweden). Small for Gestational Age (SGA) was defined as birth weight below the 10th percentile for the general population.

Statistical analysis

Data were analyzed by using SPSS Statistical software (version 24.0 for Windows, SPSS, Chicago, Illinois, USA) and R (version 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) at a given day, unless otherwise specified.

In order to assess possible attrition bias due to discontinuation of plasma glucose monitoring in infants without hyperglycemia before reaching the age of 28 postnatal days, student t-test was used to compare the frequency of glucose testing in two sub-groups: (1) infants who were treated at one 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 weekly basis among surviving infants in the respective week. Rates of hyperglycemia were compared between the groups using a chi-square 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 one single day, or during two or three 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 two groups: Region group 1 - where insulin was given more often (treatment rate $\geq 20\%$; $N = 314$; 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 with hyperglycemia > 180 mg/dL (10 mmol/L) occurring during the first 28 postnatal days and insulin treatment was further adjusted for intraventricular hemorrhage (IVH) occurrence (grades 3-4), Clinical Risk Index for Babies (CRIB) score, diagnosis of necrotizing enterocolitis (NEC), all defined according to the patient's journal, and for region group.

The significance level was set to $P < .05$.

Results

In total, 580 infants with 9850 days with plasma glucose measurements were included in the analysis. Patient characteristics are described in Table 1.

Prevalence and duration of hyperglycemic events

Seventy percent of the infants experienced hyperglycemia at some point and 44 % of the infants had hyperglycemia for 2 consecutive days during the first 28 postnatal days. Mean daily highest glucose values ranged between 122 mg/dL (6.8 mmol/L; day of birth) and 162 mg/dL (9.0 mmol/L; day 12). In general, a trend of increasing mean glucose values was noted during the first two postnatal weeks, followed by a slow decrease (Figure 1A). The occurrence of hyperglycemia followed a similar pattern, increasing from 13 % on the day of birth to 30 % of the infants tested for glucose on day 12 of life (Figure 1B). Over 20 % had hyperglycemia as late as week four of life.

Among the hyperglycemic infants, 25.9 % (105 infants) were born SGA. No significant difference in hyperglycemia rate was found between infants born SGA and non-SGA infants (71.9 % vs 69.1 %, respectively; $P = .53$)

In our cohort, 14 % of the infants were treated with insulin infusion during the first 28 postnatal days (Table 2). Administration of insulin treatment increased from less than 1 % of the cohort on the day of birth to almost 5 % of the cohort on day 14 of life (Figure 1B). The percentage of insulin treatment began to decrease slowly thereafter. Approximately 5 % of the infants who had hyperglycemia at the day of birth received insulin treatment as opposed to almost 60 % of the hyperglycemic infants at postnatal day 25 (Figure 1B). Insulin-treated hyperglycemic infants had significantly lower gestational age at birth (24.5 weeks vs 25.2 weeks), lower birth weight (647 g vs 744 g), higher CRIB score (8.7 vs 6.9) and needed mechanical ventilation for a longer period (all $P < .001$), compared with hyperglycemic

infants who did not receive insulin treatment. No differences were noted with regards to sex, NEC, IVH grades 3-4, days of antibiotics treatment or number of confirmed sepsis events.

No statistically significant differences in hyperglycemia rates were found between hospital A (where infants were frequently tested for glucose) and hospitals B-G (rest of the cohort), despite significant differences in the frequency of glucose testing between the groups (Tables 3 and 4; online).

Association between nutritional intakes and plasma glucose concentrations

During the first 28 postnatal days, there was a gradual increase of enteral carbohydrate intake and a corresponding decrease in parenteral nutritional supply (Figure 2; online). A significant positive association was found between carbohydrate intake (parenteral as well as total) and plasma glucose concentration: an increase of 1-3 % in plasma glucose concentration for every increase of 1 g/kg/d in the parenteral and total carbohydrate intakes, adjusted for birth weight and gestational age ($P < .001$).

In a model that included parenteral nutritional supply of all macronutrients, there was an increase of 1.6 % ($P < .001$) and a decrease of 3.1 % ($P < .001$) and 1.4 % ($P = .01$) in plasma glucose concentration for every increase of 1 g/kg/d in the parenteral carbohydrate, lipid and protein intakes, respectively, adjusted for birth weight and gestational age. Similar results were found when limiting the analysis only to days where the nutritional intake was more than 75 % parenteral (not shown).

A model that included the total intakes of all macronutrients showed an increase of 3.0 % ($P < .001$), a decrease of 0.3 % ($P = .20$) and an increase of 0.8 % ($P = .12$) in plasma glucose concentration for every increase of 1 g/kg/d in the total carbohydrate, lipid and protein intakes, respectively, adjusted for birth weight and gestational age.

Daily highest glucose concentrations were not associated with the number of culture-verified sepsis events or the duration of antibiotic treatment.

Hyperglycemia and mortality

Hyperglycemia occurring at some point during the first 28 postnatal days was associated with higher 28-day mortality by a multiplicative factor of 2.45, adjusted for gestational age and birth weight (B 0.897; $P = .006$). Similar results were shown for hyperglycemia lasting for 2 consecutive days during the first 28 postnatal days, with increased 28-day mortality by a multiplicative factor of 2.55, adjusted for gestational age and birth weight (B 0.935; $P = .005$).

Insulin treatment and mortality

Receiving insulin treatment during the first 28 postnatal days was associated with lower 28- and 70-day mortality in infants who had hyperglycemia lasting for 1 day and for 2 and 3 consecutive days during this period (Table 5). Similar results were shown for infants who had hyperglycemia > 216 mg/dL (12 mmol/L) irrespective of the duration of hyperglycemia.

When comparing all infants from Region group 1 (hospitals where insulin use was more common; 29 % of hyperglycemic infants treated, proportion of treated infants: 26 % - 34.3 %) with Region group 2 (hospitals where insulin use was sparse; 8.2 % of hyperglycemic infants treated, proportion of treated infants: 0 % - 11.5 %), no significant site effect was found on either 28-day or 70-day mortality.

Treating infants who had hyperglycemia > 180 mg/dL (10 mmol/L) at some point during the first 28 postnatal days with insulin was associated with lower 28- and 70-day mortality when further adjusting for IVH, CRIB, NEC and region group (28-day mortality: OR 0.15, 95% CI 0.04-0.53, $P = .003$; 70-day mortality: OR 0.339, 95% CI 0.14-0.85, $P = .02$).

Discussion

This study shows that hyperglycemia is a common finding in extremely preterm infants. The prevalence of hyperglycemia peaks at 30 % towards the end of the second postnatal week but continues to be relatively high (approximately 20 %) even during week four of life.

As the preterm infant stabilizes, it is less common in the clinical routine to control plasma glucose frequently. Very few studies have investigated glucose concentrations in EPT infants beyond the first postnatal week.

Hays et al. has showed that 57 % of extremely low birth weight infants (< 1000 g) had persistent blood glucose concentrations > 150 mg/dL (8.3 mmol/L) during the first postnatal week and 32 % had glucose concentrations > 250 mg/dL (13.8 mmol/L) (8). In another study, 35% of 216 infants born < 1000 g had hyperglycemia > 200 mg/dL (11 mmol/L) requiring insulin treatment during the first 10 postnatal days (20). Blanco et al. published results from a retrospective study including 169 infants born < 1000 g, where 88% of the infants had glucose concentrations > 150 mg/dL (8.3 mmol/L) on at least 2 different occasions during the first 2 postnatal weeks (21). Hyperglycemic infants reached peak plasma glucose concentrations on day 6 of life on average and remained hyperglycemic for 3.7 days.

Chaves-Valdez et al. has published data where approximately 80 % of infants born < 1000 g had hyperglycemia $\geq$ 150 mg/dL (8.3 mmol/L) at some point during the first 30 postnatal days (22). Our results correspond well with these findings with hyperglycemia > 180 mg/dL (10 mmol/L) occurring in 70 % of the infants at some point during the first 28 postnatal days.

In a study including 23 infants born < 1000 g, 35% had recurrent episodes of glucose concentrations > 150 mg/dL (8.3 mmol/L) at postmenstrual age of 32 weeks and 48% had glucose concentrations > 200 mg/dL (11.1 mmol /L) (23).

To the best of our knowledge, our study is the largest done in EPT infants with regards to hyperglycemia in early life. Our results show that hyperglycemia in EPT infants is a common finding well beyond the first postnatal week. The mechanisms are not clear and might be related to immature response of the hepatocyte to the circulating insulin concentrations during hyperglycemia which leads to continued glucose production (24). Intrauterine growth might contribute to hyperglycemia, but SGA infants in our study did not experience hyperglycemia more often than non-SGA infants. Another possible, and perhaps parallel, explanation is the immaturity of the pancreatic β cells which results in inadequate insulin production (25,26). Hyperglycemia in EPT infants was previously associated with lower levels of adiponectin, possibly as a result of adipose tissue immaturity (27). These theories could not be tested in the study design presented here and therefore, further studies are needed to determine the hormonal interplay and its effect on the glucose homeostasis in the extremely preterm infant.

We also show that about half of the infants who have hyperglycemia at postnatal weeks 3-4 receive insulin treatment while very few hyperglycemic infants receive insulin during the first postnatal week. This might reflect a clinical “watchful wait” approach with regards to insulin treatment while monitoring glucose concentrations and the duration of hyperglycemia.

Contrary to what most clinicians might expect, we found that glucose infusion rate and carbohydrate intake in general had very little effect on plasma glucose concentrations. These results are supported by earlier findings by Pertierra-Cortada et al. where the majority of hyperglycemia events were not related to carbohydrate intake (4). Beardsall et al. did not find any significant association between hyperglycemia and increasing rates of dextrose infusion (1). In a study by Blanco et al., iatrogenic hyperglycemia explained only 21 % of hyperglycemia episodes and no difference in glucose infusion rates was found between hyperglycemic and euglycemic infants (21). On the other hand, Stensvold et al. did find a higher proportion of hyperglycemia among infants who received early enhanced parenteral

nutrition (28). However, we present here that even during days with a predominantly parenteral intake, glucose and other macronutrient intakes had only a small effect on glucose concentrations, and hyperglycemia was common even after the first postnatal week, a period in which the parenteral carbohydrate intake is usually low.

A limitation of our study is the inability to account for the exact time passed between the administration of nutrition and the time of every single glucose measurement the following day, which might have affected the magnitude of the association presented. A possible explanation for our results can be that the clinical decision to adjust the intake according to the plasma glucose concentration might have introduced a bias in the results. However, we have minimized this possible bias by using carbohydrate intake given during the 24-hour period immediately preceding the plasma glucose measurement. We have also excluded from these analyses days in which the infant received insulin treatment which otherwise would have affected the glucose concentrations. These results add weight to the growing body of evidence that hyperglycemia among EPT infants is not solely the result of the nutritional regimen. The nutritional intakes, especially the parenteral, affect glucose concentrations but the magnitude of this effect seems to be low and further studies are needed to clarify the factors behind hyperglycemia in this population.

We found a significant negative association between parenteral lipid intake and glucose concentrations. This was surprising since several other studies have shown the opposite (1,29). One possibility is that our observation is a chance finding caused by collinearity among the parenteral macronutrient intakes. These conflicting results call for further research to provide new knowledge regarding the effects of parenteral lipid intake on glucose metabolism in the extremely preterm infant.

Our observation of a glucose-lowering effect of parenteral amino acid intake is consistent with previously published results by te Braake et al. (30), and is possibly caused by an insulinogenic effect of some amino acids.

It has been shown that extremely low birth weight infants with hyperglycemia > 180 mg/dL (10 mmol/L) during the first postnatal week have increased mortality (31). Severe hyperglycemia (> 216 mg/dL (12 mmol/L) on 2 occasions three hours apart) during the first postnatal week is an independent risk factor for death (28). Alexandrou et al. showed that hyperglycemia during the first 24 hours of life was associated with mortality before term age (10). Our study shows that hyperglycemia > 180 mg/dL (10 mmol/L) during the first 28 postnatal days is associated with more than a two-fold increase in 28-day mortality.

The role of insulin treatment and its possible detrimental effects has been debated. Most interesting is our finding that insulin treatment during the first 28 postnatal days is associated with lower 28- and 70-day mortality in hyperglycemic EPT infants. This association was shown for different hyperglycemia definitions and durations. These results counter the results previously published by Beardsall et al. who found an increased 28-day mortality rate among very low birth weight infants treated with insulin during the first postnatal week (32). This difference might stem from the preventive approach of the insulin treatment in the aforementioned study, where an insulin dose of 0.05 units/kg/h was given to all infants from the first postnatal day, as opposed to our study, where infants received insulin treatment only if they were hyperglycemic.

A limitation of this retrospective, observational study is that residual confounding cannot be excluded. Due to the observational design, the results presented here represent associations and not necessarily cause-and-effect relations.

This study shows that hyperglycemia in EPT infants during the first 28 postnatal days is common, only modestly affected by carbohydrate intake, and associated with increased mortality. Insulin treatment in hyperglycemic EPT infants during this period was associated with lower mortality. Our results highlight the potential clinical importance of the timing of insulin treatment and of defining threshold glucose concentrations for using insulin, if indicated. Randomized controlled trials that compare different administration timings and treatment thresholds as well as different dosage regimens are warranted.

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Table 1. Patient characteristics.

Table 2. Insulin infusion treatment characteristics.

Table 3, online. Frequency of testing for plasma glucose concentrations in a sub-sample compared to the rest of the cohort (calculated for surviving infants in the respective weeks).

Table 4, online. Occurrence of hyperglycemia in frequently-tested infants compared to the rest of the cohort (calculated for surviving infants in the respective weeks).

Table 5. Logistic regression predicting the association between insulin treatment during the first 28 postnatal days and 28- and 70-day mortality in infants qualifying for different hyperglycemia definitions during the first 28 postnatal days (adjusted for gestational age and birth weight).

Figure 1. A. Mean daily highest (in red, upward-pointing triangles) and lowest (in blue, downward-pointing triangles) glucose plasma concentrations and 95% confidence intervals during the first 28 postnatal days. B. Daily occurrence of hyperglycemia among tested infants (in red, line 1), daily occurrence of insulin treatment in the cohort (in blue, line 2) and daily occurrence of insulin treatment in infants with hyperglycemia the same day (in green, line 3) during the first 28 postnatal days.

Figure 2, online. Mean daily enteral (in blue, upward-pointing triangles), parenteral (in red, downward-pointing triangles) and total (in black squares) carbohydrate intakes and 95% confidence intervals during the first 28 postnatal days.

Table 1. Patient characteristics.

	The entire cohort	Infants with hyperglycemia	Infants without hyperglycemia	<i>P</i>
	Mean (SD)	Mean (SD)	Mean (SD)	
Gestational age, <i>weeks</i>	25.3 (1.1)	25.1 (1.1)	25.9 (0.8)	< .001*
Birth weight, <i>grams</i>	763 (168)	725 (163)	852 (147)	< .001*
CRIB score (<i>N</i> = 570)	7 (4)	7 (3)	5 (4)	< .001*
	Median (Range)	Median (Range)	Median (Range)	
Mechanical ventilation during postnatal days 0-28, <i>number of days</i>	7 (0-28)	11 (0-28)	3 (0-28)	< .001**
Sepsis episodes during postnatal days 0-28, <i>number of episodes</i>	0 (0-2)	0 (0-2)	0 (0-2)	.17**
Antibiotics treatment during postnatal days 0-28, <i>number of days</i>	7 (0-23)	7 (0-23)	7 (0-21)	.02**
	Number (%)	Number (%)	Number (%)	
Number of infants	580	405	175	
Males	317 (54.7)	231 (57)	86 (49.1)	.08*
Severe IVH (grade 3-4)	78 (13.4)	55 (13.6)	23 (13.1)	.89*
NEC	33 (5.7)	24 (5.9)	9 (5.1)	.70*

Hyperglycemia – glucose concentration measurement > 180 mg/dL (10 mmol/L) at some point during the first 28 postnatal days

* Student t-test

** Wilcoxon-Mann-Whitney test

Table 2. Insulin infusion treatment characteristics.

Number of infants treated with Insulin (% of cohort)	80 (13.8)
Total number of days of Insulin treatment in the cohort	604
Median number of treatment days per child (range)	4.5 (1-28)
Median day of life for beginning of Insulin treatment (range)	7 (0-26)
Mean daily dose given, in units/kg/h (SD)	0.06 (0.052)
25 th percentile	0.02
50 th percentile	0.04
75 th percentile	0.07

Table 3. Frequency of testing for plasma glucose concentrations in a sub-sample compared to the rest of the cohort (calculated for surviving infants in the respective weeks).

	Days per week with glucose values		95% CI of the difference	<i>P</i> *
	Hospital A	Hospitals B-G		
Week 1 of life (N=543)	6.86	6.03	0.66-1.00	< .001
Week 2 of life (N=523)	6.88	4.39	2.25-2.73	< .001
Week 3 of life (N=516)	6.37	3.54	2.38-3.28	< .001
Week 4 of life (N=513)	5.88	2.88	2.42-3.57	< .001

* Student t-test

Table 4. Occurrence of hyperglycemia in frequently-tested infants compared to the rest of the cohort (calculated for surviving infants in the respective weeks).

	Prevalence of hyperglycemia, %		<i>P</i> *
	Hospital A	Hospitals B-G	
Week 1 of life (<i>N</i> =543)	52.3 (<i>N</i> =34)	50.2 (<i>N</i> =240)	.75
Week 2 of life (<i>N</i> =523)	47.7 (<i>N</i> =31)	42.1 (<i>N</i> =193)	.40
Week 3 of life (<i>N</i> =516)	35.4 (<i>N</i> =23)	32.2 (<i>N</i> =145)	.60
Week 4 of life (<i>N</i> =513)	34.4 (<i>N</i> =22)	25.6 (<i>N</i> =115)	.14

* Chi-square test

Table 5. Logistic regression predicting the association between insulin treatment during the first 28 postnatal days and 28- and 70-day mortality in infants qualifying for different hyperglycemia definitions during the first 28 postnatal days (adjusted for gestational age and birth weight).

Hyperglycemia definition	Duration of hyperglycemia	Mortality among treated	Mortality among untreated	OR	95% CI	P
28-day mortality						
> 180 mg/dL (10 mmol/L)	1 day	3/80 (3.8%)	42/325 (12.9%)	0.180	0.05-0.61	.006
	2 days	2/77 (2.6%)	22/175 (12.6%)	0.138	0.03-0.61	.009
	3 days	2/65 (3.1%)	15/99 (15.2%)	0.139	0.03-0.65	.01
> 216 mg/dL (12 mmol/L)	1 day	2/78 (2.6%)	30/228 (13.2%)	0.122	0.03-0.53	.005
	2 days	2/70 (2.9%)	14/98 (14.3%)	0.138	0.03-0.65	.01
	3 days	2/50 (4.0%)	8/40 (20.0%)	0.160	0.03-0.92	.04
70-day mortality						
> 180 mg/dL (10 mmol/L)	1 day	7/80 (8.8%)	50/325 (15.4%)	0.375	0.16-0.88	.02
	2 days	6/77 (7.8%)	28/175 (16%)	0.342	0.13-0.88	.03
	3 days	4/65 (6.2%)	19/99 (19.2%)	0.228	0.07-0.72	.01
> 216 mg/dL (12 mmol/L)	1 day	6/78 (7.7%)	37/228 (16.2%)	0.317	0.13-0.80	.02
	2 days	5/70 (7.1%)	19/98 (19.4%)	0.263	0.09-0.76	.01
	3 days	3/50 (6.0%)	10/40 (25.0%)	0.182	0.04-0.77	.02

Figure 1

A

B

Figure 2