Early Insulin Therapy in Very-Low-Birth-Weight Infants

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ABSTRACT

BACKGROUND

Studies involving adults and children being treated in intensive care units indicate that insulin therapy and glucose control may influence survival. Hyperglycemia in very-low-birth-weight infants is also associated with morbidity and mortality. This international randomized, controlled trial aimed to determine whether early insulin replacement reduced hyperglycemia and affected outcomes in such neonates.

METHODS

In this multicenter trial, we assigned 195 infants to continuous infusion of insulin at a dose of 0.05 U per kilogram of body weight per hour with 20% dextrose support and 194 to standard neonatal care on days 1 to 7. The efficacy of glucose control was assessed by continuous glucose monitoring. The primary outcome was mortality at the expected date of delivery. The study was discontinued early because of concerns about futility with regard to the primary outcome and potential harm.

RESULTS

As compared with infants in the control group, infants in the early-insulin group had lower mean (±SD) glucose levels (6.2±1.4 vs. 6.7±2.2 mmol per liter [112±25 vs. 121±40 mg per deciliter], P=0.007). Fewer infants in the early-insulin group had hyperglycemia for more than 10% of the first week of life (21% vs. 33%, P=0.008). The early-insulin group had significantly more carbohydrate infused (51±13 vs. 43±10 kcal per kilogram per day, P<0.001) and less weight loss in the first week (standard-deviation score for change in weight, −0.55±0.52 vs. −0.70±0.47; P=0.006). More infants in the early-insulin group had episodes of hypoglycemia (defined as a blood glucose level of <2.6 mmol per liter [47 mg per deciliter] for >1 hour) (29% in the early-insulin group vs. 17% in the control group, P=0.005), and the increase in hypoglycemia was significant in infants with birth weights of more than 1 kg. There were no differences in the intention-to-treat analyses for the primary outcome (mortality at the expected date of delivery) and the secondary outcome (morbidity). In the intention-to-treat analysis, mortality at 28 days was higher in the early-insulin group than in the control group (P=0.04).

CONCLUSIONS

Early insulin therapy offers little clinical benefit in very-low-birth-weight infants. It reduces hyperglycemia but may increase hypoglycemia (Current Controlled Trials number, ISRCTN78428828.)

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NITIAL STUDIES OF ADULTS RECEIVING intensive care suggested that insulin therapy and improved glycemic control reduced morbidity and mortality,[1] but subsequent studies have shown variable responses to insulin therapy, and hypoglycemia may be an important risk factor.[2,3] In very-low-birth-weight (<1500 g) infants, especially those born small for gestational age, the incidence of hyperglycemia is high (20 to 86%)[4,5] and is associated with both mortality and morbidity.[6,7] These infants might therefore also benefit from insulin therapy and tighter glycemic control. Insulin therapy is often used in neonatal units, but few prospective studies have assessed benefits.[8-14] Preliminary results suggest efficacy with respect to improved weight gain and the reduced incidence of sepsis.[10,11,13]

The pathogenesis of hyperglycemia in very-low-birth-weight infants is complex[15] and may differ from that in adult patients receiving intensive care. Intracellular glucose deprivation, a consequence of low postnatal insulin levels,[16] may initiate counterregulatory responses and catabolism, leading to hyperglycemia.[5] A pilot study exploring whether early insulin replacement prevents catabolism indicated that neonates with early insulin treatment had lower glucose levels and better growth in leg length over the first week of life.[13] This pilot study also indicated that such an intervention increased serum levels of insulin-like growth factor I (IGF-I), which might decrease the development of retinopathy of prematurity and enhance postnatal brain growth.[17,18] The pilot study led to the present trial: Neonatal Insulin Replacement Therapy in Europe (NIRTURE).

METHODS

STUDY POPULATION

Very-low-birth-weight infants who met predefined eligibility criteria were recruited between 2005 and 2007 from eight neonatal intensive care centers. These centers were located in Cambridge, Edinburgh, Leeds, and Luton (United Kingdom); Leuven and Genk (Belgium); Amsterdam; and Barcelona. Infants younger than 24 hours of age were included if their birth weight was less than 1500 g, they required intensive care, and their parents provided written informed consent. Exclusion criteria were maternal diabetes and major fetal congenital abnormalities. Infants were followed to the expected date of delivery.

The study was an international, open-label, randomized, controlled trial. Randomization was achieved with the use of a 24-hour Internet-based program (www.thesealedenvelope.com) that used minimization to reduce variability according to center, birth weight (<1000 g or 1000 to 1500 g), and gestational age (<25 weeks or ≥25 weeks). Infants were randomly assigned to a study group as soon as possible during the first day of life. Blinding of the treatment allocation was not feasible, since it would not achieve adequate differences in glucose control between the groups and might reduce patient safety. Ethical and regulatory authority approval (EudraCT number, 2004-002170-34) was obtained for each center, and the protocol is in the public domain.[19] The trial was monitored and coordinated by the Clinical Trials Unit of the British Society for Paediatric Endocrinology and Diabetes in Cambridge, United Kingdom, in accordance with international guidelines.[20] An independent data and safety monitoring committee, appointed by the trial steering committee, met at least every 6 months to review the data and determine the need for interim analyses according to a formal charter of the data and safety monitoring committee.[21] The study sponsor was Cambridge University Hospitals National Health Service Foundation Trust. Novo Nordisk donated the insulin aspart, and Medtronic donated the continuous glucose-monitoring equipment. Neither Novo Nordisk nor Medtronic had any role in the design of the study, the gathering of data, access to data, the preparation of the manuscript, or the decision to publish the results.

INTERVENTION

Management of glucose control in both study groups was predetermined in the protocol[19] and implemented through standard operating procedures. Central venous access was required for the per-protocol infusion of parenteral nutrition and 20% dextrose; thus, only infants with extant central access were considered for inclusion in the study.

Early-Insulin Group

Infants who were randomly assigned to the early-insulin group received a fixed-dose continuous infusion of insulin (0.05 U per kilogram per hour), with additional intravenous 20% dextrose to maintain euglycemia (target range, 4 to 8 mmol per

liter [72 to 144 mg per deciliter]) from within 24 hours after birth until 7 days of age. Insulin aspart (Novo Nordisk) was used, since this insulin analogue has a short half-life.[22,23] Dextrose was infused if blood glucose levels decreased to less than 4.0 mmol per liter (72 mg per deciliter), starting at 1 ml per kilogram per hour,[19] and insulin was discontinued if this infusion did not prevent a drift toward hypoglycemia (<2.6 mmol per liter [47 mg per deciliter]).[19] If there was persisting hyperglycemia (>10 mmol per liter [180 mg per deciliter]), rates of infusion of glucose were reduced or additional insulin was infused.

Control Group

Infants who were randomly assigned to the control group received standard care in which the physician who was responsible for clinical care reviewed glucose levels that were greater than 10 mmol per liter (180 mg per deciliter) or less than 2.6 mmol (47 mg per deciliter). The physician would determine whether the rate of infusion of dextrose should be reduced or increased or if insulin therapy should be initiated. Insulin was initiated only after two glucose levels were greater than 10 mmol per liter with the use of a sliding scale and an initial dose of 0.05 U per kilogram per hour.

GLUCOSE MONITORING

The glucose response was recorded in all infants by continuous subcutaneous glucose monitoring.[5] The continuous glucose monitoring system (CGMS Gold, Medtronic) includes a disposable glucose oxidase–based platinum electrode sensor that was inserted by hand into subcutaneous tissue in the lateral thigh. Some infants required replacement of the sensor because it failed or became dislodged, but the sensor was not replaced more than once in any of the infants. This sensor catalyzes interstitial glucose, generating an electrical current recorded on a monitor as an averaged glucose value every 5 minutes. Glucose values outside the range of 2.2 to 24 mmol per liter (40 to 400 mg per deciliter) were recorded as less than 2.2 mmol per liter or more than 24 mmol per liter, respectively. The monitor was calibrated at least thrice daily with the use of a blood sample measured with the device normally used on each unit for the clinical management of glucose; a combination of arterial, venous, or capillary samples was used. The data from the continuous glucose monitoring system were not viewed in real time;

thus, clinical care of the study infants was based on standard blood glucose monitoring. Data obtained from continuous glucose monitoring in each infant were downloaded at completion of the 7-day study period. Glucose levels in infants in the early-insulin group were checked hourly after insulin was initiated, but the time interval was increased to every 6 hours once glucose levels had stabilized. Glucose levels in infants in the control group were measured as clinically indicated, at least thrice daily (every 8 hours).[19]

STUDY DESIGN

The study aim was to determine whether early introduction of fixed-dose insulin replacement, with variable dextrose support, to maintain euglycemia (4 to 8 mmol per liter), as compared with standard reactive management of glucose control, would improve glycemic control and thus reduce morbidity and mortality at the expected date of delivery. Hyperglycemia was defined as a glucose level of more than 10 mmol per liter and hypoglycemia as a glucose level of less than 2.6 mmol per liter on the basis of data from continuous glucose monitoring. The primary outcome measure was the effect of early-insulin therapy on mortality, before the expected date of delivery. The ranked secondary outcome measures were the incidence of sepsis in the first 2 weeks of life, somatic growth at 28 days, the incidence of necrotizing enterocolitis at 28 days, the occurrence of retinopathy of prematurity (stages 3 through 5), the incidence of intracranial disease (assessed centrally by an investigator blinded to the treatment assignment), mortality at 28 days of age, and the number of days of intensive care. Definitions of some of the secondary outcomes are provided in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

SAMPLE SIZE

The sample size was based on the primary outcome measure: mortality at the expected date of delivery, which was estimated to be 20% in the control group. To detect an absolute difference of 10 percentage points with 80% power at the 5% level of significance, approximately 430 infants would be needed; thus, allowing for withdrawal of patients from the study, we aimed to recruit 500 patients. However, recruitment was suspended by the trial steering committee after 389 infants had been enrolled, after a recommen-

dation of the data and safety monitoring committee suggesting that analysis of the centralized cranial ultrasound images revealed an excess of ventricular hemorrhage and parenchymal lesions and a trend toward more deaths in the early-insulin group. Although there was no statistical difference in the prespecified secondary outcome of ultrasound evidence of intracranial disease, the recommendation of the data and safety monitoring committee was based on a combination of futility associated with the primary outcome and concern about potential harm. After this suspension, the trial steering committee recommended that the trial be discontinued on the grounds of futility.

STATISTICAL ANALYSIS

Intention-to-treat analyses were used to compare the early-insulin and control groups to determine event rates and odds ratios with 95% confidence intervals, with adjustment for known confounders such as gestation and birth weight.[24] We also performed prespecified secondary as-treated analyses (defined by treatment exposure for at least 4 days) in the subgroup of infants weighing less than 1 kg. Adjusted odds ratios for categorical outcomes were computed with the use of logistic regression, and adjusted differences for continuous outcomes were computed with the use of multiple regression. Analyses were performed with the use of SPSS software, version 14.0.

RESULTS

RECRUITMENT

The parents of 513 eligible infants were approached regarding the participation of their infants in the study; 389 parents (76%) provided consent, and their infants underwent randomization. The parents of 454 eligible infants were not approached regarding inclusion of their infants in the study because the mother was too unwell or was offsite, the baby did not require intensive care, or the clinician was not available to allow consent to be obtained. Figure 1 shows the enrollment of infants in the study. Although the case mix differed among centers, the overall assignment of infants to the early-insulin and control groups was balanced according to the gestational age, standard-deviation score for birth weight, Clinical Risk Index for Babies (CRIB) score (scores range from 0 to 23, with higher scores indicating

more severe illness),[25] presence or absence of prolonged rupture of membranes, presence or absence of chorioamnionitis, and receipt or nonreceipt of antenatal glucocorticoids (Table 1).

Among the 389 infants recruited, 6 of 195 assigned to the early-insulin group (3%) never received insulin, and 9 were subsequently withdrawn from the study intervention. A total of 13 infants in the early-insulin group (7%) did not receive the full intervention (at least 4 days of treatment) either because the insulin was not initiated on day 1 (in 1 infant), or was discontinued because of a lack of central venous access (in 5), recurrent hypoglycemia (in 3), or death that was not associated with hypoglycemia (in 4).
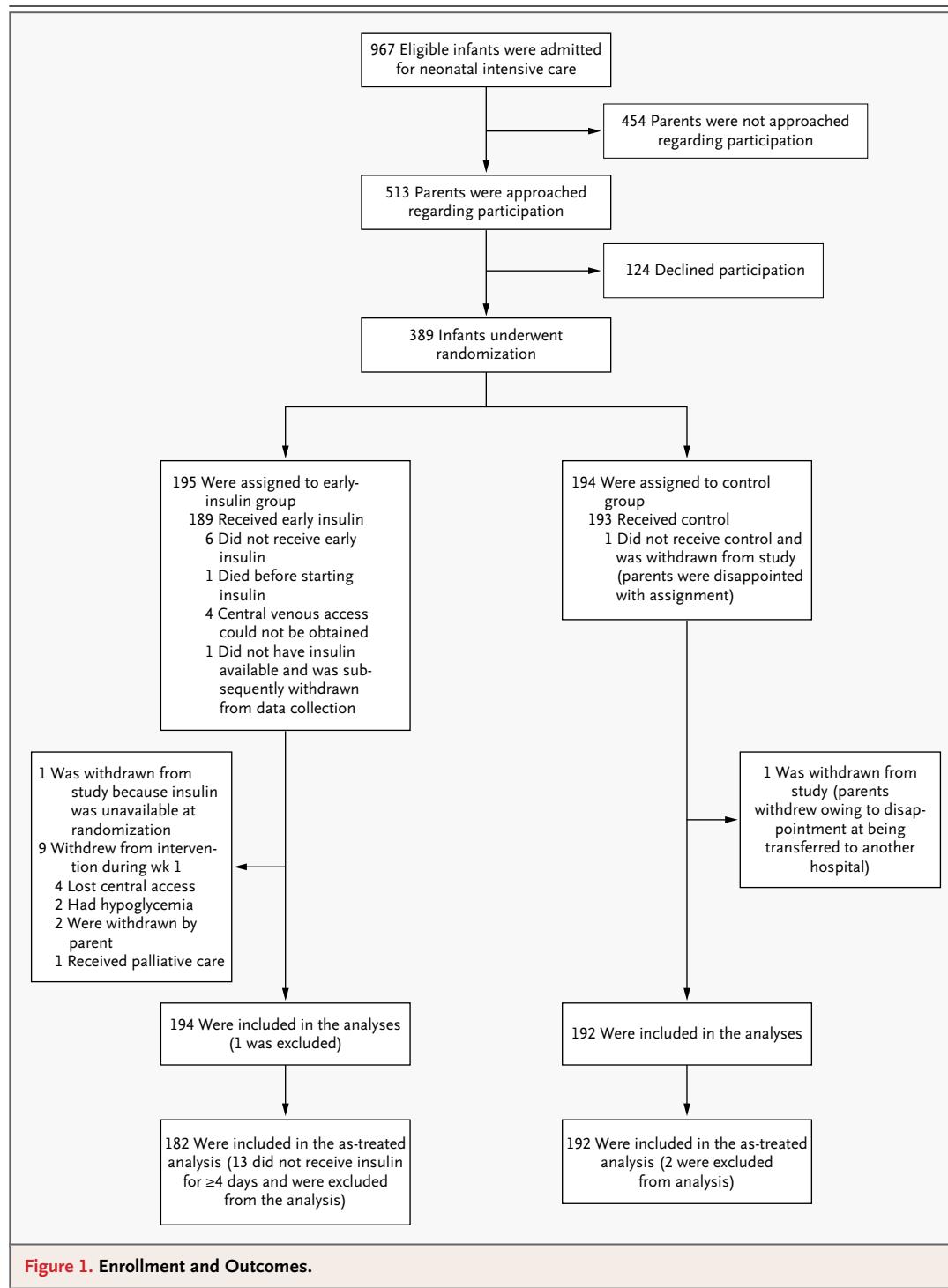
In the early-insulin group, the median (interquartile range) time to the initiation of insulin therapy was 13 hours (range, 5 to 20). Insulin therapy was initiated in 69 infants in the control group (36%) during the first week, in accordance with standard clinical care, and in these infants the median time to the initiation of insulin therapy was 3 days (interquartile range, 1 to 4).

GLUCOSE CONTROL

Continuous glucose monitoring showed a mean (±SD) daily glucose level of 6.7±2.2 mmol per liter (121±39.6 mg per deciliter) in the control group and 6.2±1.4 mmol per liter (112±25.2 mg per deciliter) in the early-insulin group (P=0.007) (Fig. 2). The proportion of infants in whom more than 10% of the glucose readings were greater than 10 mmol per liter was 33% in the control group and 21% in the early-insulin group (odds ratio, 0.42; 95% confidence interval [CI], 0.25 to 0.72; P=0.002). Overall, more infants in the early-insulin group had a documented episode of hypoglycemia (29%, vs. 17% in the control group; odds ratio, 2.21; 95% CI, 1.34 to 3.65; P=0.005). In prespecified subgroup analyses, the increase in hypoglycemia was significant only in the infants with a birth weight of more than 1 kg (34%, vs. 12% in the control group; odds ratio, 3.96; 95% CI, 1.85 to 8.47; P<0.001). There was no increase in hypoglycemia in infants with a birth weight of less than 1 kg (26% in the early-insulin group vs. 23% in the control group; odds ratio, 1.17; 95% CI, 0.60 to 2.28; P=0.7).

NUTRITIONAL INTAKE

During the 7-day intervention period, significantly more intravenous carbohydrate was infused in

Figure 1. Enrollment and Outcomes.

the early-insulin group than in the control group (51±13 kcal per kilogram per day vs. 43±10 kcal per kilogram per day; P<0.001). However, there were no differences between the study groups with regard to rates of either protein or lipid infusion (Table 2).

MORTALITY

There was no difference in the outcome of mortality at the expected date of delivery (18 of 192 infants in the control group [9%] vs. 28 of 194 infants in the early-insulin group [14%]; odds ratio, 0.61; 95% CI, 0.33 to 1.15; P=0.2; and ab-

Table 1. Baseline Clinical Characteristics of Infants and Mothers at Recruitment.*

Variable	Control Group (N = 192)	Early-Insulin Group (N = 194)
Infants		
Gestational age at birth — wk	27.8±2.2	27.6±2.2
Birth weight — kg	1.009±0.274	1.007±0.267
Head circumference — cm	25.4±2.3	25.3±2.2
Crown–heel length — cm	35.4±3.6	35.3±3.7
Birth weight — standard-deviation score	–0.91±1.1	–0.84±1.1
Sex — no. (%)		
Male	95 (49)	101 (52)
Female	97 (51)	93 (48)
CRIB score†	4.02±3.4	3.99±3.5
Mothers		
PROM — no. (%)	49 (26)	48 (25)
Receipt of antenatal glucocorticoids — no. (%)	176 (92)	178 (92)
Chorioamnionitis — no. (%)	33 (17)	32 (16)

* Plus–minus values are means ±SD. Data are presented for all infants included in the analyses. There were no statistically significant differences between the two study groups. CRIB denotes Clinical Risk Index for Babies, and PROM prolonged rupture of membranes.

† CRIB scores range from 0 to 23, with higher scores indicating more severe illness.

solute difference, 5.1%; 95% CI, –1.4% to 11.5%; P=0.16). After adjustment for prenatal variables (i.e., the presence or absence of maternal chorioamnionitis, the presence or absence of prolonged rupture of membranes, use or nonuse of antenatal glucocorticoids, CRIB score, gestational age, and standard-deviation score for birth weight), the odds ratio for the primary outcome was not substantially altered (odds ratio, 0.53; 95% CI, 0.26 to 1.09; P=0.08).

Prespecified subgroup analyses involving infants weighing less than 1 kg as compared with infants weighing more than 1 kg showed no significant unadjusted or adjusted difference in mortality according to gestational age and standard-deviation score for birth weight. The as-treated analysis showed no significant unadjusted or adjusted difference in mortality at the expected date of delivery (Table 3). The secondary outcome, death before 28 days after birth, occurred in 5.7% of infants in the control group (11 of 192) as compared with 11.9% in the early-insulin group (23 of 194); this difference was significant (P=0.04), even after adjustment for gestational age and standard-deviation score for birth weight (odds ratio, 0.38; 95% CI, 0.17 to 0.88; P=0.02).

The most common causes of death before 28 days were overwhelming infection and extreme prematurity. However, in subsequent as-treated analyses, mortality was 10.4% (19 of 182 patients) among patients in the early-insulin group; this rate was not significant as compared with the rate among controls (odds ratio, 0.52; 95% CI, 0.24 to 1.12; P=0.13) (Table 4).
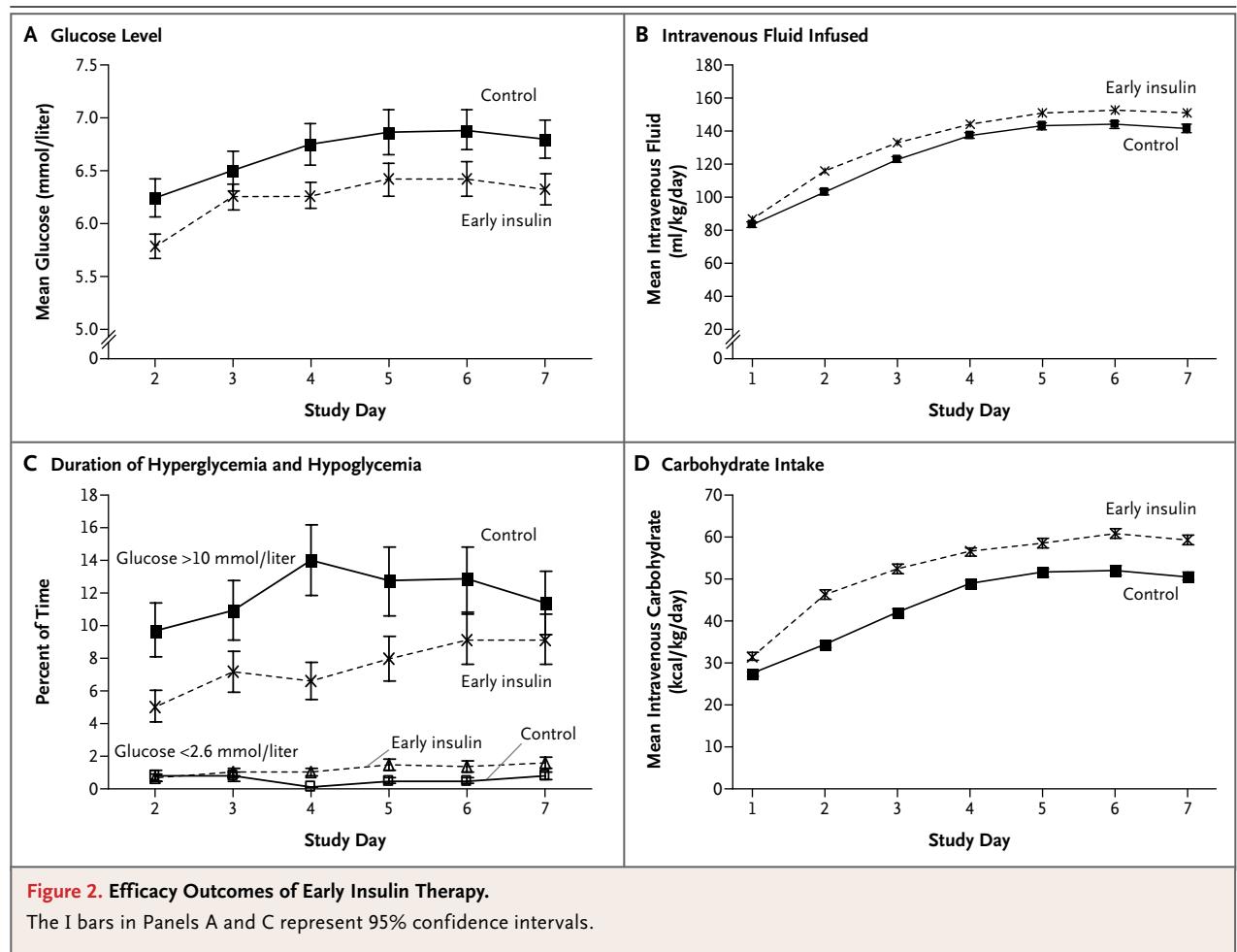
MORBIDITY

The proportions of infants with each of the pre-specified secondary outcomes were similar in the two groups (Table 3). Adjusting for prenatal variables (i.e., the presence or absence of maternal chorioamnionitis, the presence or absence of prolonged rupture of membranes, and the use or nonuse of antenatal glucocorticoids), and for CRIB score, as well as for gestational age and standard-deviation score for birth weight, had no significant effect on any of the secondary morbidity outcomes. There were no differences between the study groups with regard to the change of standard-deviation score for weight, length, or head circumference during the period between birth and 28 days. However, there was less weight loss during the first week after birth in the early-insulin group (mean [±SD] change in standard-deviation score for weight, –0.55±0.52 vs. –0.70±0.47; P=0.006); this was equivalent to a weight difference of 31 g.

ADVERSE EVENTS

All reported major adverse events, apart from hypoglycemia, were related to the primary or secondary outcomes. There were no reported adverse events relating to trauma, infection, or edema associated with the continuous glucose-monitoring sensor. No unanticipated serious adverse reactions were suspected. Clinicians reported episodes of hypoglycemia (blood glucose <2.6 mmol per liter for >1 hour), in 17 infants in the early-insulin group (8.8%) (including 2 who had protocol violations and 4 who were withdrawn from the study) and in 3 in the control group (1.6%). Episodes of hypoglycemia were not associated with clinical signs of hypoglycemia.

DISCUSSION

This international trial showed that the use of elective early insulin therapy in very-low-birth-weight infants may lead to a significant improvement in glucose control and an increase in energy

1878

Figure 2. Efficacy Outcomes of Early Insulin Therapy.

The I bars in Panels A and C represent 95% confidence intervals.

intake during the first week of life. There were no differences between the two study groups with regard to the primary outcome of mortality at the expected date of delivery or to morbidity outcomes. Intention-to-treat analyses showed an increase in mortality at 28 days, although this finding was not significant in the as-treated analyses. There was an increased risk of hypoglycemia among infants in the early-insulin group, and longer-term follow-up of the cohort will be required to evaluate the full importance of these findings.

Although this study showed that early insulin therapy can reduce the prevalence of hyperglycemia, the differences in the levels of glucose control between the study groups was not as large as in the pilot study.[13] Furthermore, we observed an increase in episodes of hypoglycemia in the early-insulin group, particularly in the infants with a birth weight of more than 1 kg; as compared with infants who weighed less, these infants had a

lower risk of hyperglycemia and were likely to be less tightly monitored. The NIRTURE study design aimed both to provide insulin replacement and to promote anabolism, while limiting the risk of hypoglycemia. Future interventional studies might benefit from focusing on extremely-low-birth-weight infants (<1 kg) who are at high risk of illness and death; these studies might use real-time glucose monitors to improve glucose control without the risk of hypoglycemia. Although in this study no episodes of hypoglycemia were reported to be associated with physiological signs, it will be important to follow these infants into childhood to review potential longer-term effects of hypoglycemia on neurocognitive outcomes.

Although there was no statistically significant difference in mortality at the expected date of delivery, the secondary outcome, death by 28 days, was significantly increased in the early-insulin group (P=0.04). Although this level of

Table 2. Insulin Therapy, Glucose Control Assessed by Continuous Glucose Monitoring, and Nutritional Intake, Week 1.*

Variable	Control Group (N = 192)	Early-Insulin Group (N = 194)	P Value
Time to initiation of insulin infusion			
Median	Day 3†	13.4 hr	
Interquartile range	Days 1–4	5.3–20.1 hr	
Mean insulin infused — U/kg/day			
Median	0.00	1.09	<0.001
Interquartile range	0.00–0.18	1.05–1.15	
Mean fluids infused — ml/kg/day	124±20	132±23	<0.001
Mean carbohydrates infused — kcal/kg/day	43±10	51±13	<0.001
Mean protein infused — g/kg/day			
Median	1.24	1.12	0.4
Interquartile range	0.2–1.9	0.2–1.8	
Mean lipids infused — kcal/kg/day			
Median	5.9	5.5	0.9
Interquartile range	0.0–13.4	0.0–12.3	
Mean milk intake — ml/kg/day			
Median	6.1	6.1	0.8
Interquartile range	2.6–13.3	2.7–10.7	
Glucose control, days 2–7‡			
Mean glucose — mmol/liter/day	6.7±2.2	6.2±1.4	0.007
Infants with glucose >10 mmol/liter for >10% of time during the first wk — no. (%)	64 (33)	40 (21)	0.008
Infants with an episode of hypoglycemia (glucose <2.6 mmol/liter) for >60 min during the first wk — no. (%)	33 (17)	56 (29)	0.005

* Plus–minus values are means ±SD.
† Data are for the 69 infants in the control group (36%) who received insulin in week 1.
‡ Data are based on values from the continuous glucose-monitoring system. To convert values for glucose to milligrams per deciliter, multiply by 18.

significance is not robust, it is, nevertheless, of concern. The prespecified as-treated analysis, excluding the 13 infants in the early-insulin group who either did not start treatment or received treatment for less than 4 days, indicated no difference in mortality (P=0.13). The major difference between the as-treated and the intention-to-treat analyses involves four infants in the early-insulin group who died before receiving 4 days' treatment; none of these infants had evidence of hypoglycemia according to continuous glucose monitoring. However, such as-treated analyses will have reduced statistical power.

Because of these potential differences in mortality and hypoglycemia between the early-insulin and control groups, the data and safety monitoring committee initiated exploration of other non–protocol-driven analyses of cranial ultrasound reports. The subsequent observation of an increased incidence of brain parenchymal lesions in the early-insulin group led to the recommendation for suspension. This finding was based on data-driven analyses of the centrally reported cranial ultrasound data, not on any of the prespecified secondary outcomes. Periventricular leukomalacia, or evidence of porencephalic cysts at that time, had been reported in 8 of 146 infants in the early-insulin group (5.5%) as compared with 1 of 151 infants in the control group (0.7%). However, the evaluation of reports based

Table 3. Study Outcomes.*

Outcome	Control Group (N = 192)	Early-Insulin Group (N = 194)	Odds Ratio	Difference between Control and Early-Insulin Groups
				value (95% CI)
Death before expected date of delivery — no. (%)	18 (9.4)	28 (14.4)	0.61 (0.33 to 1.15)	
Sepsis, first 2 wk — no. (%)				
Culture-positive	44 (22.9)	41 (21.1)	1.11 (0.69 to 1.8)	
Presumed	55 (28.6)	53 (27.3)	1.07 (0.69 to 1.67)	
Necrotizing enterocolitis, first 28 days — no. (%)	22 (11.5)	23 (11.9)	0.92 (0.49 to 1.71)	
Retinopathy of prematurity ≥stage 3 — no./total no. (%)†	15/173 (8.7)	16/165 (9.7)	0.88 (0.42 to 1.84)	
Intracranial disease (0 vs. 1–4) — no./total no. (%)‡	58/181 (32.0)	64/176 (36.4)	0.83 (0.53 to 1.28)	
Chronic lung disease — no./total no. (%)	52/174 (29.9)	55/166 (33.1)	0.85 (0.54 to 1.35)	
Death before 28 postnatal days — no. (%)	11 (5.7)	23 (11.9)	0.45 (0.21 to 0.96)	
Growth between birth and 28 postnatal days				
Change in weight — g	284±138	302±146		18 (–12 to 48)
Change in length — cm	3.2±1.9	3.1±1.9		–0.1 (–0.5 to 0.4)
Change in head circumference — cm	1.9±1.1	2.0±1.1		0.2 (–0.1 to 0.4)
Neonatal intensive care — days	19.2±17.4	16.9±15.5		–2.4 (–6.0 to 1.3)

* Plus–minus values are means ±SD. Comparative data for all infants are included in the analyses. Data on intracranial disease are from cranial ultrasound scans reviewed and reported at a central site. Odds ratios greater than 1 indicate a positive effect of the intervention. See the Supplementary Appendix for definitions of the outcomes.
† The stages of retinopathy of prematurity range from 1 to 4, with higher numbers indicating worse disease.
‡ The grades of intracranial disease range from 0 to 4, with higher numbers indicating worse disease.

on real-time ultrasound scans obtained clinically did not show any statistically significant difference in intracranial disease.

This study has certain limitations. The early discontinuation of the study may have reduced statistical power, and the difference in glycemic control between the early-insulin and control groups was small. Furthermore, 36% of the infants in the control group received insulin to treat hyperglycemia. However, in the pilot study, the administration of insulin in control patients was shown to be less efficacious than early insulin in improving glucose control.[13] Tighter glucose control may have improved clinical outcomes. However, aims to achieve tighter glucose control must be balanced against the risk of hypoglycemia and its potential effect on long-term neurologic outcomes.[26,27]

Although intervention improved glucose control, increased energy intake, and reduced weight loss in the first week of life, the failure to show differences in the prespecified secondary morbidity outcomes, including growth at 28 days, is disappointing. These results might be due to the intervention period of only 7 days. Possibly, more sustained insulin replacement would be required to affect longer-term anabolism. However, although infants in the early-insulin group received more energy, their protein intake during the first week (mean, 1.23 g per kilogram per day) was substantially less than may be needed to achieve clinically important growth (3.5 g). However, these levels of protein intake are typical of current standard clinical practice,[28] and there is no evidence that the intervention limited protein intake. Protein intake is usually increased as tolerated, with a target of 3.5 g per kilogram per day being reached by the end of the first week of life.[29] It is widely acknowledged that optimal nutrition is often difficult to achieve in the early neonatal period, and the amount received is often less than that prescribed. If insulin replace-

Table 4. Subgroup Analyses.*

Variable	Control Group (N=192)	Early-Insulin Group (As-Treated Analysis) (N=182)	Odds Ratio *value (95% CI)*	Difference between Control and Early-Insulin Groups *value (95% CI)*	Control Group (Infants <1 kg) (N=97)	Early-Insulin Group (Infants <1 kg) (N=97)	Odds Ratio *value (95% CI)*	Difference between Control and Early-Insulin Groups *value (95% CI)*
Death before expected date of delivery — no. (%)	18 (9.4)	24 (13.2)	0.68 (0.36 to 1.30)		16 (16.5)	21 (21.6)	0.71 (0.34 to 1.45)	
Sepsis in first 2 wk — no. (%)								
Culture-positive	44 (22.9)	41 (22.5)	1.02 (0.63 to 1.66)		31 (32.0)	25 (25.8)	1.33 (0.71 to 2.49)	
Presumed	55 (28.6)	50 (27.5)	1.06 (0.67 to 1.66)		32 (33.0)	35 (36.1)	0.86 (0.47 to 1.55)	
Necrotizing enterocolitis in first 28 days — no. (%)	22 (11.5)	21 (11.5)	0.96 (0.51 to 1.82)		17 (17.5)	12 (12.4)	1.40 (0.62 to 3.13)	
Retinopathy of prematurity ≥stage 3 — no./total no. (%)†	15/173 (8.7)	16/157 (10.2)	0.84 (0.40 to 1.75)		12 (12.4)	12 (12.4)	0.90 (0.38 to 2.15)	
Intracranial disease (0 vs. 1–4) — no./total no. (%)‡	58/181 (32.0)	62/169 (36.7)	0.81 (0.52 to 1.27)		34 (35.0)	33 (34.0)	1.01 (0.55 to 1.85)	
Chronic lung disease — no./total no. (%)	52/174 (29.9)	55/158 (34.8)	0.80 (0.50 to 1.27)		37 (38.1)	38 (39.2)	0.84 (0.45 to 1.58)	
Death before 28 postnatal days — no. (%)	11 (5.7)	19 (10.4)	0.52 (0.24 to 1.12)		9 (9.3)	16 (16.5)	0.51 (0.21 to 1.22)	
Growth between birth and 28 postnatal days								
Change in weight — g	284±138	298±147		5 (−29 to 39)	214±91	237±122		23 (−10 to 56)
Change in length — cm	3.2±1.9	3.1±1.9		−0.1 (−0.56 to 0.40)	2.7±1.4	3.1±1.7		0.4 (−0.11 to 0.95)
Change in head circumference — cm	1.9±1.1	2.0±1.1		0.00 (−0.25 to 0.26)	1.6±1.1	1.9±1.2		0.29 (−0.08 to 0.67)
Neonatal intensive care — days	19.2±17.4	17.3±15.7		−1.8 (−6.0 to 2.5)	29±16.1	28±16.5		−1.15 (−6.5 to 4.2)

* Plus–minus values are means ±SD. Comparative data are provided for infants in the as-treated analysis and infants with a birth weight of less than 1 kg. Data on intracranial disease are from cranial ultrasound scans reviewed and reported at a central site. Odds ratios of greater than 1 indicate a positive effect of the intervention. See the Supplementary Appendix for definitions of the outcomes.

† The stages of retinopathy of prematurity range from 1 to 4, with higher numbers indicating worse disease.

‡ The grades of intracranial disease range from 0 to 4, with higher numbers indicating worse disease.

ment is to promote anabolism during early postnatal life, optimal protein and energy balance needs to be achieved, since the balance between growth and adiposity may have important implications for long-term metabolic outcomes.[30]

Our study reflects the current controversies regarding the role of insulin and improved glucose control in intensive care. Some studies have shown dramatic improvements in clinical outcomes,[1] but results have not been consistent,[31] and this treatment is not without risk.[3] Although the reasons that adults require intensive care are very different from the problems of prematurity that lead to neonatal intensive care, some of the physiological mechanisms that link adverse outcomes to both hypoglycemia and hyperglycemia are likely to be similar. In particular, concerns about the risks of hypoglycemia are clearly relevant to very-low-birth-weight infants.

The results of this early-insulin intervention study are largely negative in that improvements in glycemic control did not have a significant impact on either primary or secondary outcomes. Furthermore, the increase in hypoglycemia, particularly in infants weighing more than 1 kg, are a cause for concern, and only long-term follow-up will resolve this issue. However, the potential to refine glucose control with the use of continuous real-time glucose monitoring would, in our view, be worth exploring. Improving dietary protein intake, along with safe insulin delivery, may improve IGF-I generation with implications for brain growth and the risk of retinopathy. Further study of IGF-I levels and long-term neurodevelopment outcomes in these populations will be critical.

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1883

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