Glucose Affects the Severity of Hypoxic-Ischemic Brain Injury in Newborn Pigs

Michael H. LeBlanc, MD; Min Huang, MD, PhD; Vibha Vig, MD; Daksha Patel, MD; Edward E. Smith, MD

Background and Purpose: The administration of glucose has been shown to worsen brain injury in adult animals but has no effect on the severity of injury in newborn rats. We wished to see whether the results in newborn rats could be extended to another newborn animal.

Methods: In 44 0- to 3-day-old piglets, hypoxic-ischemic central nervous system damage was induced by ligation of both carotid arteries and reduction of their blood pressure to two-thirds normal for one-half hour. In the last 15 minutes of this half hour, oxygen concentration was reduced to 6%. The piglets were randomized to receive either 2 mL/kg 50% dextrose in water followed by 2 mL/kg per hour for 2.5 hours beginning before ischemia or enough insulin to reduce their resting blood sugar to approximately 2 mmol/L.

Results: Neurological exam scores in the glucose-treated piglets at 1 day after injury were significantly worse than those in the insulin-treated group. Pathological examination scores were poorer in the glucose-treated group (13.6±1.9 [mean±SEM]) than in the insulin-treated group (24.7±1.4, P<.01).

Conclusions: Increasing serum glucose during hypoxic-ischemic injury to the newborn piglet's brain worsens brain injury. (Stroke 1993;24:1055-1062)

Key words: glucose • hypoxia • insulin • pigs

M yers et al showed that juvenile monkeys subjected to elevated blood glucose levels during hypoxic-ischemic brain injury had severe damage. It has been hypothesized that this injury is due to high levels of lactic acid building up in the brain cells, which causes low intracellular pH values and thereby disrupts cellular machinery. Despite enhanced cellular energy stores during hypoxic ischemia in the glucose-treated animals, brain damage was worse and was associated with higher intracellular lactic acid levels. There have been concerns that this might not apply to newborns. Voorhies et al showed that giving glucose to 1-week-old rats did not increase brain injury. Studies in newborns of other animal species have not yet been performed. These data from a single species have been used to justify the routine use of glucose-containing intravenous fluid for pregnant women in labor. We have performed a series of experiments using an identical protocol to evaluate drugs to ameliorate hypoxic brain injury in newborn pigs. Because we accumulated over this series of experiments a large number of control animals in which systemic parameters were looked at, we attempted to correlate these parameters with pathological outcome. The strongest predictor of pathological outcome was serum glucose level: Piglets with higher glucose levels had worsened neurological outcomes (r=.48, P<.0001). However, correlation with outcome does not prove causation because glucose might well be a marker for another factor. We observed at the same time that the older animals had both higher serum glucose and more severe brain damage, but the correlation between age and brain damage was less tight than between serum glucose and brain damage. Thus, we set out to determine whether differences in glucose level, randomly assigned as an experimental variable, would affect the severity of hypoxic-ischemic brain damage in our newborn pig model.

In the human newborn, unlike the human adult, most clinical injury to the brain is initiated as an asphyxial or hypoxic event of variable acuity. Injury is usually global rather than focal. There is usually some secondary brain ischemia due to hypoxic dysfunction of the heart. However, it is difficult to generate reproducible hypoxic brain injury in a purely hypoxic model without an unacceptable death rate from hypoxic myocardial damage. Thus, an ischemic component—clamping both carotid arteries and reducing the blood pressure by one third—was added to the hypoxic insult to reliably produce measurable brain injury with acceptable mortality. We arrived at the particular timing of the ischemic and hypoxic components through a series of pilot experiments.

Materials and Methods

Using our previously described protocol, 44 0- to 3-day-old piglets were removed from their mother the day of the experiment and randomly assigned to either
a glucose- or insulin-treated group (Fig 1). They were anesthetized with 1.5% isoflurane and 50% nitrous oxide, intubated, and ventilated with a Harvard rodent ventilator adjusted to obtain an initial Pco₂ of approximately 5.3 kPa (40 mm Hg). Catheters were placed in the superficial artery of the right rear leg and in the right external jugular vein using sterile technique. A snare was placed around both carotid arteries. Electroencephalographic (EEG) needle electrodes were placed beneath the periosteum in the right and left parietal regions, with a ground lead placed at the base of the snout. EEG was recorded at 20 μV/cm. After surgery was completed, the isoflurane was reduced to 0.5%, and the animal was paralyzed with an infusion of 0.5 mg/kg per minute of succinylcholine. Both isoflurane and nitrous oxide have effects on cerebral blood flow and metabolism and the response of the brain to ischemia,12,13 as do most anesthetics. Each animal’s rectal temperature was maintained at 38.0°C using a servocontrolled infrared lamp.

After the initial surgery was performed, the piglets assigned to the glucose group received 2 mL/kg IV of 50% dextrose in water followed by a continuous infusion of 2 mL/kg per hour for 2 hours after reoxygenation. In the piglets assigned to the insulin group, serum glucose levels were checked with Glucostix (Miles Inc, Elkhart, Ind) immediately after the initial surgery. The piglets with an initial glucose level of greater than 3.9 mmol/L received 2 U/kg of regular porcine insulin IV push. They were then observed for 15 minutes, and their serum glucose levels were rechecked. If the glucose level remained over 5.6 mmol/L, an additional dose of 2 U/kg insulin was given, and the animals were monitored an additional 15 minutes to ensure that their serum glucose levels went below 5.6 mmol/L. At time −5 minutes, baseline measurements were taken. The measurements included arterial blood gases, arterial blood pressure, rectal temperature, oral temperature, whole-blood lactate, and serum glucose. This set of measurements was repeated at 0, 15, 30, 45, 60, and 90 minutes. At time 0, 700 U/kg heparin was injected, and the carotid arteries were ligated by pulling the snare snugly around them. Blood was withdrawn from the arterial catheter into syringes to reduce the arterial pressure to approximately two thirds of control levels and maintain it at that level. Isoflurane was discontinued at 10 minutes, by which time the animals had been rendered unconscious by the ischemia (pilot studies). Fifteen minutes after the carotid ligation and the reduction of blood pressure to two thirds of normal, the animal was switched from ventilation with 50% nitrous oxide and 50% oxygen to a gas mixture containing 70% nitrous oxide, 22% nitrogen, 2% carbon dioxide, and 6% oxygen. This reduced arterial Po₂ to approximately 3.3 kPa (25 mm Hg) within 1 to 2 minutes. Approximately 2 minutes after hypoxia, the animal’s EEG tracing became totally flat. Succinylcholine was discontinued at 20 minutes (it is required until this time to prevent gasping). At an experimental time of 30 minutes, after 15 minutes of hypoxia, the animal was reoxygenated by switching the inspired gas from 6% to 100% oxygen, releasing the carotid ligatures, and reinfusing the blood that had been previously withdrawn. The effect of reoxygenation with 100% oxygen on neurological outcome of hypoxic ischemia is controversial.14,15 We confirmed at autopsy that patency of the carotids was reestablished. Immediately before reoxygenation, blood β-hydroxybutyrate levels were measured by enzymatic assay in a subgroup using a kit from Sigma Chemical Co, St Louis, Mo.

Piglets were nursed in cages, with warmth provided by heat lamp. From 2 to 17 hours after reoxygenation, they received 5% dextrose at 8 mL/h IV. They were then fed 60 cm³ artificial piglet formula by gavage every 6 hours. Neurological examination was performed by the staff performing the experiment at 2 hours after reoxygenation. Neurological examinations were performed by a blinded observer at 1, 2, and 3 days after reoxygenation. The results were recorded and scored from 0 to 20, with 20 considered normal and 5 brain dead according to a standard scoring system (Table 1).

Three days after the experiment, with the pig under isoflurane and nitrous oxide anesthesia, the chest was opened, the carotid artery was cannulated, and the brain was perfused with 10% formalin after flushing with 30 mL saline. Formalin was continued until the effluent from the right atrium was clear, thus preserving the brain and killing the animal. The brain was then removed and preserved in formalin for later pathological examination. If the piglet died before completion of the 3 days, its carcass was stored in the refrigerator until the next morning, when a gross autopsy was performed and the brain was preserved in formalin.

After preservation in formalin, the brains of all piglets were cut, fixed, and stained. A coronal section was taken at the level of the optic chiasm and another approximately 3 mm back to demonstrate the cerebral cortex, hippocampus, and basal ganglia. Paraffin sections were stained with hematoxylin and eosin and
TABLE 1. Piglet Neurological Examination

I. Mental status
   (subtract 1 for seizures)
   Coma (no responsiveness) 1
   Stupor (responsiveness to vigorous stimulation only with posturing) 2
   Lethargy (drowsiness or delirium) 3
   Awake 4
   
   Subtotal
   Subscore (subtotal)

II. Cranial nerves
A. Pupils
   Unreactive 1
   Sluggish 2
   Normal 4
B. Corneals
   Absent 1
   Present 4
C. Occulovestibular
   Absent 1
   Present 4
D. Suck
   Absent 1
   Present 4

   Subtotal
   Subscore (subtotal/4)

III. Reflexes
A. Deep tendon
   Absent 1
   Hyper 2
   Normal 4
B. Stepping
   Absent 1
   Present 4
C. Righting
   Absent 1
   Present 4

   Subtotal
   Subscore (subtotal/3)

IV. Motor
A. Unable to stand 1
B. Bears weight with abnormal posture 2
C. Gets to standing with difficulty 3
D. Stands normally 4

   Subtotal
   Subscore (subtotal)

V. Coordination
A. No attempt to walk 1
B. Attempts to walk but can’t 2
C. Walks but falls 3
D. Walks normally 4

   Subtotal
   Subscore (subtotal)

Score (sum of subscores)

Score of 20 is considered normal; score of 5, brain dead.

TABLE 2. Pathological Scoring System

<table>
<thead>
<tr>
<th>Score</th>
<th>Cellular change</th>
<th>Area affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>Hypoxic</td>
<td>Few cells</td>
</tr>
<tr>
<td>8</td>
<td>Hypoxic</td>
<td>Scattered cells</td>
</tr>
<tr>
<td>7</td>
<td>Hypoxic</td>
<td>&lt;33% area</td>
</tr>
<tr>
<td>6</td>
<td>Hypoxic</td>
<td>33% to 66% area</td>
</tr>
<tr>
<td>5</td>
<td>Hypoxic</td>
<td>66% to 100% area</td>
</tr>
<tr>
<td>4</td>
<td>Necrotic</td>
<td>Scattered cells</td>
</tr>
<tr>
<td>3</td>
<td>Necrotic</td>
<td>&lt;33% area</td>
</tr>
<tr>
<td>2</td>
<td>Necrotic</td>
<td>33% to 66% area</td>
</tr>
<tr>
<td>1</td>
<td>Necrotic</td>
<td>66% to 100% area</td>
</tr>
</tbody>
</table>

examined by light microscopy. Each section was graded on a scale of 1 to 10 (Table 2), with a score of 10 considered normal by a pathologist blinded to the experimental group of the piglets. Cellular changes were classified as hypoxic (considered by the pathologist to be potentially reversible, with scores of 5 to 9, depending on size of involved area) or necrotic (thought to be clearly irreversible, with scores of 1 to 4, depending on size of involved area). The final score was the sum of the scores of each of the three tissues. Hypoxic changes were largely shrunken hyperchromatic neurons but also included enlarged perivascular spaces and eosinophilic staining neurons with pyknotic nuclei; necrotic changes included loss of neurons with glial and vascular proliferation and increased macrophage activity in the tissue.

Arterial whole blood lactate was measured enzymatically. Arterial serum glucose was measured by the glucose oxidase technique. Blood gases and pressures were measured by standard techniques. Comparisons were made between the glucose and insulin groups using a t test (two-tailed) for continuous variables and the Mann-Whitney U test for ordinal variables. Comparisons with controls from previous experiments were made using analysis of variance or Kruskal-Wallis when appropriate. All results are presented as mean±SE, with P<0.05 considered nonsignificant.

Results

Piglets in the glucose-treated group (n=22) weighed 1522±64 g and were 1.6±0.2 days old. Those in the insulin-treated group (n=22) weighed 1569±76 g and were 1.8±0.2 days old, not significantly different from the values in the glucose group. Values for arterial pH, arterial Pco2, temperature (rectal and oral), and heart rate were not statistically significantly different in the two groups (Fig 2). Arterial blood pressure was comparable in the two groups until 60 minutes. It was slightly but significantly (P<.05) higher in the glucose-treated group at 60 and 90 minutes (Fig 3). Arterial Po2 was significantly higher at 15 and 60 minutes in the glucose-treated group (P<.05, Fig 3). Arterial Po2 levels at −5, 0, 30, 35, 45, and 90 minutes were not significantly different in the two groups. Blood lactate levels were not statistically significantly different in the two groups (Fig 3). Serum glucose level was significantly (P<.0001) higher at all time periods in the glucose-treated than in the control group (Fig 3).
Neurological examination scores are shown in Table 3. There was no difference between the two groups at 2 hours, 48 hours, or 72 hours. The neurological examination scores at 24 hours were significantly (P<.01) worse in the glucose-treated group. Neurological examination scores on sham piglets not subjected to hypoxic-ischemic injury (n=10) were 19.9±0.1, as previously reported. 10

Fifteen (68%) of the piglets in the glucose-treated group died before euthanasia, whereas only nine (41%) in the insulin control group died early (.05<P<.1). The time of death in the pigs that died before euthanasia was 18±5 hours in the glucose-treated group (n=15) and 25±6 hours in the control group (n=9) (P=not significant [NS]). Pathological examination scores are shown in Table 4. In the upper half of the table, the

<table>
<thead>
<tr>
<th>Time of examination</th>
<th>Glucose-treated</th>
<th>Insulin-treated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Score</td>
</tr>
<tr>
<td>2 Hours</td>
<td>22</td>
<td>10.0±0.5</td>
</tr>
<tr>
<td>1 Day</td>
<td>10</td>
<td>11.8±1.2</td>
</tr>
<tr>
<td>2 Days</td>
<td>9</td>
<td>13.6±1.3</td>
</tr>
<tr>
<td>3 Days</td>
<td>7</td>
<td>13.3±1.5</td>
</tr>
</tbody>
</table>

Values are mean±SEM. n, Number of piglets.
*Score of 20 is considered normal; 5, brain dead.
‡P<.01 vs insulin.
values for all the pigs are shown; in the lower half of the table, values are shown only for the pigs that survived the full 72 hours and received brain preservation at death. Values for the cortex, hippocampus, and basal ganglia are given in addition to the value for the sum of the scores for the three tissues. Representative histological sections are shown in Figs 4 and 5. In all cases, the scores in the glucose-treated group were significantly worse ($P<.01$) than those in the insulin-tested piglets. Pathological examination results in sham piglets not subjected to hypoxic-ischemic injury were as follows: cortex ($n=11$), 9.0±0.1; basal ganglion ($n=11$), 9.7±0.2; hippocampus ($n=11$), 9.8±0.1; and sum ($n=11$), 28.5±0.3, as previously reported.

Both groups in this experiment received some treatment. To determine which of the treatments resulted in the differences seen, the pathological examination scores for the two groups were compared with pathological examination scores from control animals from previous experiments. These control animals were subjected to the protocol described in “Materials and Methods” to induce hypoxic-ischemic injury but were not given any treatment (ie, no glucose or insulin). They were examined by the same pathologist used in this experiment. Glucose values in this control group ($n=66$) were 4.2±0.2 mmol/L, 6.3±0.4 mmol/L, and 7.5±0.6 mmol/L at 0, 15, and 30 minutes, respectively (at 0 and 15 minutes, $P<.01$ vs glucose and $P<.01$ vs insulin; and at 30 minutes, $P<.01$ vs glucose and NS vs insulin). Values at other times are included in the referenced papers.

Pathological scores in the insulin-treated animals were significantly better ($P<.01$) and pathological scores in the glucose-treated group significantly worse ($P<.05$) than scores seen in the historic control group (hypoxia-ischemia alone; see Table 2, column 3).

The correlation between the glucose concentration measured at 30 minutes and the pathological score is shown in Fig 6 (Path=$25-0.44$ [Glucose]; $r=0.45$, $P<.002$). Higher-order polynomial terms were not statistically significant. β-Hydroxybutyrate levels were
0.25±0.08 mmol/L in the glucose group (n=5) and 0.09±0.05 mmol/L in the insulin group (n=6) (P=.09).

Discussion

Elevating glucose levels during injury worsens injury to the brain in juvenile and adult animals. Although increasing blood glucose during hypoxic-ischemic injury to adult animals results in elevated brain energy levels, the resulting increased brain lactic acid levels and decreased intracellular pH cause irreversible injury before damage by energy depletion alone. The adverse effect of administered glucose may be prevented by glycolytic blockage. It may be demonstrated by administering glucose to elevate normal glucose levels or by using insulin to diminish normal glucose levels. In newborn animals, results in the 1-week-old rat showed that increasing glucose levels by administering glucose had no effect on the degree of hypoxic-ischemic brain injury. The lack of effect of glucose in the neonatal rat model seemed to be due to decreased ability to transport and metabolize glucose in the brain so that elevated serum glucose levels did not increase brain lactate levels during hypoxic ischemia to the brain.

The newborn piglet, like the newborn human and the 1-week-old rat, is in the period of maximal brain growth. In that sense, both should be good models for human newborns. The results of the present study suggest that there are species differences in the ability of glucose to worsen injury to the brain of the newborn animal. These results suggest that newborns of some species are capable of transporting and metabolizing enough glucose in the brain to result in damage due to excess lactate concentrations. Glucose and lactate levels in the brain were not measured in this experiment; however, as shown by Corbett et al piglets during cardiac arrest, maximal lactic acid levels in the brain during ischemia are directly related to serum glucose levels in the piglet regardless of age. The adaptation of the 1-week-old rat to a very high-fat, low-carbohydrate diet may explain the peculiarities of this species regarding glucose transport and metabolism. The brain of the 1-week-old rat metabolizes mostly ketone bodies rather than glucose. Does the glucose metabolism of the brain of human newborns more closely resemble that of the 1-week-old rat or the newborn pig? In the 1-week-old rat, glucose transport to the brain is very low relative to adult rat levels and is functioning near saturation. Thus, under the stress of hypoxia, lactic acid production is limited and is not increased if additional glucose is available. On the other hand, piglets produce higher brain lactic acid levels during hypoxia, when glucose levels are elevated. Data from human infants are sketchy, but glucose transport levels down to 5 days of age in human infants are similar to those in human adults and would not seem to restrict brain lactic acid production. Thus, the available data suggest that the handling of glucose by the brains of human infants is more like that of newborn pigs than 1-week-old rats. In human infants of insulin-dependent mothers, the de-
gree of maternal hyperglycemia at delivery is a better predictor of perinatal asphyxia than are more chronic measures of maternal glycemic control (ie, glycohemoglobin-A1c). This association is consistent with the hypothesis that in human infants, hyperglycemia during hypoxic-ischemic brain injury is detrimental to the brain.

There are several methodological differences between the 1-week-old rat model in which no effect of glucose is seen and our neonatal pig model in which glucose concentration strongly affects the outcome of hypoxic-ischemic brain injury. The 1-week-old rat model produces focal injury to one hemisphere of the brain, whereas the neonatal pig model produces global brain injury. In adult animals, both global and focal21 brain injury are worsened by glucose, so this is unlikely to explain the difference seen. The 1-week-old rat model has a prolonged (3-hour) period of moderate hypoxia (8% oxygen) and mild ischemia (unilateral carotid ligation without hemorrhage), whereas the neonatal pig model has a short period of severe hypoxia (6% oxygen for 15 minutes) and moderate ischemia (bilateral carotid clamping with hemorrhage to two thirds of normal blood pressure for 30 minutes). A prolonged period of hypoxia might allow lactic acid levels to equilibrate with serum35 and avoid excessive brain levels. Lactic acid–induced brain injury is thought to be a threshold phenomenon requiring concentrations in excess of 20 μmol/g for brain injury to occur.36 Respiration and blood pressure are controlled in the neonatal pig model but not in the 1-week-old rat model. In experiments performed on newborn rhesus monkeys, glucose administered with alkali prolonged cardiac function during asphyxia37 and reduced the severity of ischemia experienced by the brain and secondarily reduced brain injury.38 In 1-week-old rats, arterial blood pressure is well preserved for the 3 hours of hypoxic ischemia39; therefore, this mechanism may not be important in the rat pup model. Glucose preserves energy stores in the brain even in species in which it worsens injury.20,21,40 and thus in some species prolongs the breathing41 during hypoxia. This may lessen damage in experimental or clinical circumstances in which apnea is important in the production of brain injury and the subjects are not mechanically ventilated. Part of the mammalian response to stress is hyperglycemia, which is caused by increased catecholamine production. What is the adaptive advantage of a system that worsens brain injury? By prolonging breathing, hyperglycemia would improve survival chances in the pre–cardiopulmonary resuscitation world. In that context, what happens after terminal apnea is not important.

In this experiment, the hyperglycemia was induced by glucose and the low glucose levels were induced by insulin. We did this because a piglet normally responds to the stress of hypoxic ischemia with hyperglycemia unless it is prevented, and we were afraid that giving only glucose would produce too small an effect to be easily detected. This was not the case. Inducing hyperglycemia with insulin significantly improved outcomes over previous control groups. Inducing hyperglycemia with glucose infusion worsened the outcome both relative to the insulin group and relative to controls that received neither insulin nor glucose. All this strongly suggests that glucose caused the change in outcomes seen in our previous experiments associated with differences in serum glucose level.8-11

How are the results of this experiment clinically applicable? Does giving intravenous dextrose to women in labor, as is commonly done in clinical practice, worsen the neurological outcome of their infants if birth asphyxia occurs? No experiments have been performed that directly answer this question. Whatever comfort previously provided by studies in rat pups is now called into question. The effect of glucose on a mammalian infant’s response to hypoxic-ischemic brain injury is species specific. Controlled studies in humans will be necessary to determine whether current obstetrical practices are harmless, harmless, or beneficial.

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15. Rootwell T, Loberg EM, Moen A, Oyaaseter S, Saugstad OD. Hypoxemia and reoxygenation with 21% or 100% oxygen in new-
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http://stroke.ahajournals.org/content/24/7/1055