WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care

Worksheet author(s) Date Submitted for review: 2-24-2009

Clinical question.

"In neonates requiring resuscitation, (P) will the early use of supplemental glucose (I) during and/or following delivery room resuscitation, versus none (C) improve outcome (i.e. avoidance of hypoglycemia, reduced longterm neurologic morbidity) (O)?"

Is this question addressing an intervention/therapy, prognosis or diagnosis? Intervention/therapy

State if this is a proposed new topic or revision of existing worksheet: Update/revision

Conflict of interest specific to this question

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? No

Search strategy (including electronic databases searched).

PubMed search terms: MeSH “resuscitation” or “asphyxia” or “asphyxia neonatorum” or “hypoxia-ischemia, brain” AND text words (glucose or hyperglycemia or hypoglycemia or insulin) AND MeSH “infant, newborn” or “animal, newborn” (MeSH)

“resuscitation” + “hypoxia-ischemia, brain” + text words (glucose or hyperglycemia or hypoglycemia or insulin) 9 hits
“asphyxia” or “asphyxia neonatorum” + (glucose or hyperglycemia or hypoglycemia or insulin) + “infant, newborn” 14 hits
“resuscitation” + (glucose or hyperglycemia or hypoglycemia or insulin) + “infant, newborn” 137 hits
“hypoxia-ischemia, brain” + (glucose or hyperglycemia or hypoglycemia or insulin) + “infant, newborn” 32 hits
“hypoxia-ischemia, brain” + (glucose or hyperglycemia or hypoglycemia or insulin) + “animal, newborn”
Web of Knowledge (ISI): (“hypoglycemia or hyperglycemia or glucose”) AND (“asphyxia or hypoxia-ischemia”) AND (“newborn or “neonat*)
Embase: (“newborn hypoxia” or “perinatal asphyxia”) AND (“hypoglycemia” or “hyperglycemia” or “blood glucose level”) and (“brain” or “outcome”) 15 unique hits

Also AHA EndNote Master library, Cochrane Database for Systematic Reviews, Central Register of Controlled Trials, DARE, review of references from key articles: No unique references found

• State inclusion and exclusion criteria

Inclusion criteria: Studies in infants, children and relevant animal models that examined the relationship between glucose levels and outcome after resuscitation or significant CNS hypoxic-ischemic event

Exclusion criteria: Studies that examined physiologic effects of interventions but did not describe a short- or long-term outcome; studies in cell culture or other laboratory systems only; studies in unrelated patient populations, i.e., adults, post-operative patients; studies that used oxygen-glucose deprivation as initial insult

• Number of articles/sources meeting criteria for further review: 28 articles included; 1 LOE 3; 3 LOE 4, and 21 LOE 5 (18 animal studies, 3 clinical retrospective studies in different population)
## Summary of evidence

### Evidence Supporting Clinical Question

<table>
<thead>
<tr>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
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<tr>
<td>Ondo-Onama E3</td>
<td>Lin E3, Salhab E3</td>
<td>Brambrink E3, Klein E3, Losek E3, Wintergerst E3</td>
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**Level of evidence**

A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = Other endpoint  

*italics = Animal studies*

**Other endpoints:**

- E1: Change in outcome if glucose level altered prior to hypoxia-ischemia
- E2: Change in outcome if glucose level altered after hypoxia-ischemia
- E3: Differences in outcome based on uncontrolled glucose levels

### Evidence Neutral to Clinical question

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<tr>
<td>LeBlanc 1994 E2, LeBlanc 1997 E1, Voorhies E1, Yager E1</td>
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- E2: Change in outcome if glucose level altered after hypoxia-ischemia
- E3: Differences in outcome based on uncontrolled glucose levels
## Evidence Opposing Clinical Question

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<thead>
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<th>Good</th>
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<th>Park 2001 E2</th>
<th>LeBlanc 1993 E1</th>
<th>Sheldon E2</th>
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E3: Differences in outcome based on uncontrolled glucose levels
REVIEWER’S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

Background: Clinical and animal studies suggest that hyperglycemia increases cerebral injury in adults after stroke, while studies in newborn animals, in contrast, suggested that hypoglycemia might worsen hypoxic-ischemic brain injury and hyperglycemia could be beneficial. More recent clinical studies in surgical ICU patients appeared to show improved outcome if glucose concentration was controlled by post-operative insulin administration; however, subsequent randomized controlled trials in critically ill adults showed no benefit and some potential harm if blood glucose was tightly controlled.

Available clinical data that address the question of optimal glucose concentration following cerebral insult in the newborn are limited. There are no randomized, controlled studies of the effect of early use of supplemental glucose on outcome following delivery room resuscitation. One case review with controls and 3 retrospective case reviews without controls (LOE 4) were identified; these studies examined associations between physiologic variables, including glucose levels, and outcome following perinatal asphyxia and resuscitation. Infants who had withdrawal of support due to severity of insult had lower blood glucose levels than less severely affected infants (Lin, 1996 LOE 4). Similarly, babies with low Apgar scores who subsequently died had a higher incidence of hypoglycemia compared to those who survived or matched controls with normal Apgars (Ondoa-Onama, 2003 LOE 3) In term infants with severe fetal acidosis, the incidence of abnormal neurologic outcome was >3-fold higher in those with hypoglycemia compared to those with “normal” glucose values (Salhab, 2004 LOE 4). Newborns with HIE and abnormal blood sugar values post-resuscitation were more likely to have abnormal imaging studies and EEGs and had lower scores on developmental assessment (Zeng, 2005 LOE 4). However, these results may reflect the fact that more severely affected infants are more likely to have a more significant disturbance of glucose homeostasis, rather than that hypoglycemia led to worse outcomes.

In critically ill children, one study found that hypoglycemia was not associated with worse outcome in PICU patients (Klein, 2008, LOE4), while a second study found that hypoglycemia, hyperglycemia, and overall variability of glucose concentration was associated with increased LOS and mortality in children in the PICU (Wintergerst, 2006, LOE 4). Mortality rate was higher in hypoglycemic children requiring resuscitation in the emergency room (Losek, 2000 LOE 4).

A number of animal studies have addressed the question of glucose or insulin administration and outcome after cerebral hypoxia-ischemia (all LOE 5). Five studies investigated the effect of hypoglycemia induced prior to exposure to hypoglycemia (Chang 1999, Park 1995, Vannucci 1978 & 1980, Yager 1992); results suggest that hypoglycemia either worsens brain injury or has no effect. In 9 studies, hyperglycemia was induced by glucose administration prior to the insult. Six found that pre-existing hyperglycemia was associated with decreased injury or decreased physiologic disturbances (Holowach 1974, McGowan 1995, Nagai 2008, Rosenberg 1990, Tuor 1993, Vannucci 1996), 2 found no effect (LeBlanc 1997, Voorhies 1986), and one found that brain injury was augmented by prior glucose administration (LeBlanc 1993). In 2 studies (Laptook 1992 & 1994), effects of pre-existing hypoglycemia were compared to those of pre-existing hyperglycemia; hypoglycemia resulted in a more profound metabolic disturbance after hypoxia-ischemia. Only 4 studies looked at glucose administration after exposure to cerebral hypoxia ischemia. Two showed apparent benefit (Hattori 1990, Park 2001), one showed no effect (LeBlanc 1994), and one showed a possible detrimental effect (Sheldon 1992).

Conclusion

DISCLAIMER: Potential possible wording for a Consensus on Science Statement. Final wording will differ due to other input and discussion.

CONSENSUS ON SCIENCE: Newborns with lower blood glucose levels have a higher incidence of brain injury and adverse outcomes after a hypoxic-ischemic insult, although no specific level that is associated with worse outcome has been identified (Lin J Perinat Med 1996 24:581 LOE 4; Ondoa-Onama East Afr Med J 2003 3:22, LOE 3; Salhab Pediatr 2004 114:361, LOE 4; Zeng Chin J Clin Rehab 2005 9:92, LOE 4). Increased glucose levels (after hypoxia-ischemia do not appear to have adverse effects in pediatric patients (Klein, J Pediatr 2008 153:379, LOE 5, blood glucose >200 mg/dl); or in animal studies (LeBlanc, Stroke 1994 25:1443 LOE 5; Voorhies Neurol 1986 36:1115, LOE 5) and may be protective (Hattori Ann Neurol 1990 28:122, LOE 5, blood glucose 450-540 mg/dl). However, there are no randomized controlled trials that examine this question. Due to the paucity of data, no specific target glucose concentration range can be identified at present.

TREATMENT RECOMMENDATION:

Acknowledgements: None
from other models of brain injury will be important to develop candidate treatment strategies for head-injured infants and predictors of outcome may also apply to pathologic conditions in the post-traumatic immature brain. Evaluation of data hypoglycemia which lasted 24 h and lactate levels were increased from 6 to 10 h after LPS administration. LPS/HI induced severe brain injury, which persisted 2 weeks after LPS/HI. Administration of glucose to LPS-treated animals asphyxia. glucose concentrations were not specifically regulated.

Chang YS, Park WS, Ko SY, Kang MJ, Han JM, Lee M, et al. Effects of fasting and insulin-induced hypoglycemia on brain cell membrane function and energy metabolism during hypoxia-ischemia in newborn piglets. Brain Research. 1999;844(1-2):135-42. This study was done to determine the effects of 12 h fasting-induced mild hypoglycemia (blood glucose 60 mg/dl) and insulin-induced moderate hypoglycemia (blood glucose 35 mg/dl) on brain cell membrane function and energy metabolism during hypoxia-ischemia in newborn piglets. Sixty-three ventilated piglets were divided into six groups; normoglycemic control (NC, n=8), fasting-induced mildly hypoglycemic control (FC, n=10), insulin-induced moderately hypoglycemic control (IC, n=10), normoglycemic/hypoxic-ischemic (NH, n=11), fasting-induced mildly hypoglycemic/hypoxic-ischemic (FH, n=12) and insulin-induced moderately hypoglycemic/hypoxic-ischemic (IH, n=12) group. Cerebral hypoxia-ischemia was induced by occlusion of bilateral common carotid arteries and simultaneous breathing with 8% oxygen for 30 min. The brain lactate level was elevated in NH group and this change was attenuated in FH and IH groups. The extent of cerebral lactic acidosis during hypoxic-ischemic insult showed significant positive correlation with blood glucose level (r=0.55, p<0.001). Cerebral Na+, K+-ATPase activity and concentrations of high-energy phosphate compounds were reduced in NH group and these changes were not ameliorated in FH or IH group. Cortical levels of conjugated dienes, measured as an index of lipid peroxidation of brain cell membrane, were significantly elevated in NH, FH and IH groups compared with NC, FC and IC groups and these increases were more profound in FH and IH with respect to NH. Blood glucose concentration showed significant inverse correlation with levels of conjugated dienes (r=-0.35, p<0.05). These findings suggest that, unlike in adults, mild or moderate hypoglycemia, regardless of methods of induction such as fasting or insulin-induced, during cerebral hypoxia-ischemia is not beneficial and may even be harmful in neonates.

LOE 5; E1; Good; Supportive. Study in newborn piglets; not asphyxia model; hypoglycemia conferred no benefit and was associated with increased oxidant injury.

Elkind S, Arvidsson P, Hagberg H, Mallard, C. The role of glucose in brain injury following the combination of lipopolysaccharide or lipoteichoic acid and hypoxia-ischemia in neonatal rats. Dev Neurosci 2004; 26:61-7. We have previously shown that lipopolysaccharide (LPS) sensitizes the immature rat brain to subsequent hypoxic-ischemic (HI) injury; however, the underlying mechanisms remain unclear. In this study, we examined the role of glucose in the sensitizing effects of LPS and lipoteichoic acid (LTA) in combination with HI in 7-day-old rats. LPS/HI resulted in hypoglycemia which lasted 24 h and lactate levels were increased from 6 to 10 h after LPS administration. LPS/HI induced severe brain injury, which persisted 2 weeks after LPS/HI. Administration of glucose to LPS-treated animals with HI reduced brain injury in the cerebral cortex and hippocampus, while striatal damage remained. LTA/HI did not affect blood glucose, lactate or brain injury. In conclusion, enhanced blood glucose levels during HI after LPS administration conferred protection in some brain regions but not in the striatum, suggesting that alterations in glucose can only partly explain the sensitizing effect of LPS.

LOE 5, E1&2, Good, supportive. Glucose administration before and after cerebral hypoxia-ischemia in newborn rats exposed to LPS reduced injury in cortex and hippocampus; suggests glucose could be protective in sepsis-induced asphyxia.

We evaluated the effect of posthypoxic glucose supplement in a neonatal hypoxic-ischemic animal model. Seven-day-old rats underwent bilateral ligation of the carotid arteries, followed by exposure to an 8% oxygen atmosphere for 1 hour. The extent of hypoxic-ischemic brain damage was assessed histologically 72 hours later. Glucose load immediately after the end of the hypoxic exposure reduced the volume of neocortical infarction to 37% of the unsupplemented value, and attenuated ischemic damage in the striatum and the dentate gyrus. At the end of the hypoxic exposure, the brain level of glucose was 0.3 mmol/kg and the level of lactate 9 mmol/kg. Glucose supplement produced a rapid rise in brain glucose level to 3 to 5 mmol/kg over the next 2 hours. Lactate in both brain and plasma gradually fell toward the baseline level during the first hour of recovery. Posthypoxic glucose supplement slightly retarded lactate restitution. At any period of this neonatal model, brain lactate levels did not exceed the toxic level, which is postulated to be responsible for cerebral infarction in adult ischemic models. These results illustrate the important role of glucose in the development of neonatal hypoxic-ischemic encephalopathy and the fact that full cortical infarction can develop even if brain lactate levels are low.

LOE 5; E2; Good; Supportive. Animal study (newborn rats) with treatment immediately after insult; demonstrated efficacy of post-insult glucose administration. Model may not be equivalent to perinatal asphyxia.

Holowach-Thurston J, Hauhart RE, Jones EM. Anoxia in mice: Reduced glucose in brain with normal or elevated glucose in plasma and increased survival after glucose treatment. Pediatric Research. 1974;8:238-43. No abstract available.

LOE 5; E1, good; supportive. Newborn mice randomized to receive glucose prior to anoxia had longer survival time.


Hypoglycemia increases the vulnerability of the perinatal brain to asphyxia, but it is not known if hypoglycemia induced changes in cerebral hemodynamics and vascular reactivity underlie this vulnerability. This study tested the hypothesis that hypoglycemia exacerbates postischemic hypoperfusion, and impairs postischemic CO2 reactivity. The authors also examined the hypothesis that postischemic hypoperfusion is associated with a reduction in the interstitial concentration of the vasodilator metabolite adenosine. Global cerebral ischemia of 10 minutes duration was induced in newborn pigs anesthetized with isoflurane by occlusion of subclavian and brachiocephalic arteries; cortical cerebral blood flow (CBF) and interstitial adenosine concentration were evaluated simultaneously using the combined hydrogen clearance/microdialysis technique. Hypoglycemia (blood glucose 25 mg/dl) was induced by regular insulin (25 IU/kg) administered intravenously 2 hours prior to induction of ischemia. In the eight normoglycemic animals, baseline CBF was 38 ± 4 ml/min/100 gm and baseline adenosine concentration was 1.2 ± 0.1 mM; in the eight hypoglycemic animals, these values were 39% (p .0.05) and 62% (p .0.05) greater, respectively, under baseline conditions. At 1 hour of postischemic reperfusion in normoglycemic animals, CBF was reduced 39% relative to the preischemic baseline (p .0.01), concomitant with a 27% reduction (p .0.05) in adenosine concentration, suggesting that this lowered concentration may underlie delayed hypoperfusion. These postischemic reductions in CBF and interstitial adenosine concentration were significantly greater in hypoglycemic animals, with CBF and adenosine concentration reduced 70% (p .0.001) and 71% (p .0.01), respectively, relative to baseline. In nine animals preischemic reactivity to hypercapnia was unaffected by hypoglycemia. Postischemic hypercapnic reactivity was retained in the eight normoglycemic animals, but was attenuated 73% (p .0.05) in hypoglycemic animals. Thus, in the newborn pig, hypoglycemia exacerbates postischemic cortical hypoperfusion and impairs postischemic cerebral vascularity reactivity to hypercapnia.

LOE 5. E1, good, supportive. Animal study (newborn piglets); preexisting hypoglycemia resulted in decreased CBF during cerebral ischemia and less hypercapnia-induced vasodilation compared to normoglycemic controls.


OBJECTIVE: To identify the frequency of hyperglycemia in children who are non-diabetic and critically ill and assess the independent effect of hyperglycemia on outcome. STUDY DESIGN: Consecutive admissions to the pediatric intensive care unit (PICU) were reviewed. The Pediatric Risk of Mortality III score (PRISM) measured patient acuity. Because maximum glucose level in the first day of PICU admission (GLFD) >200mg/dL contributes to PRISM, 200 mg/dL was used to differentiate high glucose (HG) from normal glucose. RESULTS: Of 1550 patients, 221 (14.3%) had HG. GLFD correlated with PRISM (r = 0.39, P <.001). Without controlling for PRISM, the HG group had more mechanical ventilation days (MVD; P < .001), longer PICU length of stay (PLOS; P < .001) and lower percent survival (P < .001) than the normal glucose group. Controlling for PRISM in survivors, GLFD was not associated with PLOS (P = .75) or with MVD (P = .06). GLFD was not significantly associated with survival (P = .76). In nonsurvivors, GLFD was not associated with PLOS (P = .19) or MVD (P = .31). CONCLUSION: When controlling for disease severity, hyperglycemia within 24 hours of PICU admission was not independently associated with increased mechanical ventilation time, length of stay, or mortality. Prospective evaluation of glycemic control in critically ill children is needed to elucidate its effects on outcome.

LOE 5; E3; Poor; Supportive. Retrospective clinical data analysis; not asphyxia/resuscitation.

BACKGROUND AND PURPOSE: During global brain ischemia or hypoxia-ischemia in adults, hyperglycemia is deleterious to the brain. In contrast, similar adverse effects have not been found in neonatal animals. This investigation examined neonatal piglets to determine if there were specific alterations of ischemic brain metabolism associated with different systemic glucose concentrations and to potentially clarify the effects of hyperglycemia during ischemia in neonates. METHODS: Two groups of animals (n = 12 in each group) were studied during partial ischemia to compare the effects of hyperglycemia (plasma glucose concentration, 258 +/- 97 mg% [mean +/- SD]) with modest hypoglycemia (plasma glucose concentration, 62 +/- 23 mg%). A broad spectrum of cerebral blood flow reduction was achieved by combining inflation of a cervical pressure cuff with varying degrees of hemorrhagic hypotension. High-energy phosphorylated metabolites, intracellular pH, and cerebral blood flow were simultaneously measured using a magnetic resonance spectroscopic technique. Brain metabolic variables (beta-ATP, inorganic phosphorus, phosphocreatine, intracellular pH) were plotted as a function of blood flow reduction during partial ischemia for each group. RESULTS: During ischemia values of cerebral blood flow were comparably distributed between groups and ranged from 15% to 110% of those of control. At a given reduction of cerebral blood flow, hyperglycemic piglets maintained a higher concentration of beta-ATP (p = 0.011) and had a smaller increase in inorganic phosphorus (p less than 0.001). At cerebral blood flow less than 50% of control, the intracellular pH of piglets with modest hypoglycemia during partial ischemia was never reduced to less than 6.46, whereas intracellular pH fell as low as 5.97 for hyperglycemic animals. CONCLUSIONS: ATP preservation may account for the differing effects of glucose during ischemia in neonates compared with adults, provided that the accentuated brain acidosis is not deleterious to neonatal brain tissue.

LOE 5; Fair; E1; Supportive. Newborn piglet model with pre-insult manipulation of glucose; hypoglycemia during partial ischemia associated with depletion of ATP and PCR in brain. Piglet model may be better than rodent models as the piglet brain is dependent on glucose while neonatal rat brain relies on fat as primary energy source for the first 7-10 days of postnatal life.


Since systemic glucose concentration is an important determinant of ischemic brain metabolism in neonates, we sought to determine if the systemic glucose concentration influences brain metabolic alterations following repeated partial ischemia. A group of hyperglycemic piglets (n = 12) were compared to a group of modestly hypoglycemic piglets (n = 12) using in vivo2H and 31P magnetic resonance spectroscopy to simultaneously measure cerebral blood flow and phosphorylated metabolites before, during and 30 min after two 10-min episodes of ischemia (i.e. Recovery 1 and 2). For both groups, β-ATP levels at Recovery 1 and 2 were lower than Control (91 ± 11 and 83 ± 15% of Control, respectively for both groups combined, P = 0.002 vs Control). Inorganic phosphorus was elevated in hyperglycemic piglets at Recovery 1 and 2 (117 ± 15 and 118 ± 10% of Control). In contrast, in modestly hypoglycemic piglets inorganic phosphorus progressively rose from Recovery 1 (131 ± 24% of Control) to Recovery 2 (149 ± 37% of Control), and differed from the hyperglycemic group (P = 0.02). These changes did not correlate with post-ischemic cerebral blood flow, cerebral O2 delivery or cerebral glucose delivery. In both groups phosphocreatine and intracellular pH returned to Control values during Recovery 1 and 2. The progressive increase in inorganic phosphorus post-ischemia in hypoglycemic piglets suggests that modest hypoglycemia during and following repeated partial ischemia adversely affects immediate brain metabolic recovery.

LOE 5; Fair; E1; Supportive. Animal study with pre-insult manipulation of glucose; did not examine neurologic or pathologic outcomes but found deleterious effect of hypoglycemia on post-ischemic brain metabolism.


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 examination 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.

LOE 5; E1; Good; Opposing. Animal study with pre-insult manipulation of glucose; no target glucose level identified for hyperglycemic animals.

BACKGROUND AND PURPOSE: Giving glucose before hypoxic ischemia worsens brain injury in piglets. Does giving glucose after hypoxic ischemia affect severity of injury? METHODS: Forty-three 0- to 3-day-old pigs were used. All piglets received 2 U/kg insulin before injury to prevent stress-induced hyperglycemia. Hypoxic ischemic brain damage was induced by clamping both carotid arteries and reducing arterial blood pressure to two thirds of normal by hemorrhage at time 0. At 15 minutes the fraction of inspired oxygen (FiO2) was reduced to 6%. At 30 minutes FiO2 was increased to 100%, the carotids were released, and the withdrawn blood was reinfused. The piglets were then randomized to receive either 2 mL/kg of 50% dextrose followed by 2 mL/kg per hour for 2 hours or an equal volume of saline. RESULTS: Neurological examination scores (20 is normal, 5 is brain dead, by blinded observer) at 1 day postinjury were similar in the two groups: glucose, median 15.5 (25th percentile, 12.2; 75th percentile, 18); controls, 15.6 (9.3, 18). Piglets were killed at 3 days with brain preservation at death. Pathological examination scores (sum of scores from cortex, hippocampus, and basal ganglia: 30 is normal, 3 is total necrosis) by blinded observer were similar in the two groups: glucose, 26 (18, 28); controls, 25 (16.5, 28); NS. CONCLUSIONS: Although elevated glucose levels during hypoxic ischemic injury worsen brain injury in the piglet, elevated glucose levels after injury do not affect the severity of the injury.

LOE 5; E2; Good; Neutral. Newborn piglet model with post-insult manipulation of glucose; glucose concentration not specifically controlled. Found no effect of glucose administration on hypoxia-ischemic brain injury.


Glucose worsens hypoxic-ischemic brain injury in 0- to 3-day-old piglets. Piglets were randomly assigned to have blood glucose increased with glucose infusion (n = 12), or decreased with insulin (n = 13), or a sham group (n = 10). In the insulin and glucose groups at time 0, both carotid arteries were clamped, and blood was withdrawn to reduce the blood pressure one third. At time 15 min FiO2 was reduced to 6%. At time 30 min cerebrospinal fluid (CSF) was taken for glutamate, and the brains were frozen. The shams had CSF removed and brains frozen without hypoxia or ischemia. Brain ATP was 1.7 +/- 0.09 mumol/g wet weight in the shams, 0.98 +/- 0.09 in the glucose group (p < 0.01 vs. sham), and 0.52 +/- 0.10 in the insulin group (p < 0.01 vs. glucose). Brain lactate levels were 4.3 +/- 1.0 mumol/g wet weight in the shams, 18.3 +/- 1.9 in the insulin group (p < 0.01 vs. sham), and 29.4 +/- 2.6 in the glucose group (p < 0.01 vs. insulin). CSF glutamate was 9.3 +/- 3.6 microM in the glucose group, 9.6 +/- 3.5 in the insulin group, and 2.2 +/- 0.9 in the shams (p < 0.05, glucose and insulin > sham). The Bmax for MK-801 binding was 2.3 +/- 0.2 pmol/mg protein in the glucose group, 2.6 +/- 0.1 in the insulin group (p < 0.05 vs. sham), and 2.0 +/- 0.2 in the shams, and the Kd was the same in the three groups (p = nonsignificant). Brain Na+,K(+)-ATPase was the same in the three groups (p = nonsignificant). Providing additional glucose preserves ATP during hypoxic-ischemic brain injury in the piglet but does not change CSF glutamate or brain-801 binding and probably worsens outcome by elevating brain lactate levels above the threshold for cellular injury.

LOE 5; Good; E1; Neutral. Animal study with pre-insult manipulation of glucose; did not look at neurologic or pathologic outcomes. Conclusion that hyperglycemia may worsen outcome because of effects on lactate levels not supported by data, merely speculative.


The objectives of this study were to analyze the influence of maternal, perinatal and neonatal factors on the neurological sequelae occurring in asphyxiated infants. The clinical records of 79 infants, 35 weeks of gestation or more, treated in the neonatal intensive care unit in whom the principal diagnosis was asphyxia, and who had no major malformation and who survived for more than 24 hours, were analyzed. Analysis of variance was used to compare neurological outcome classified as 1) normal development or mild neurological sequelae, 2) moderate to severe neurological sequelae, and 3) withdrawal of treatment because of signs and symptoms of severe brain damage. The group in whom treatment was withdrawn had lower mean arterial blood pressure on admission, blood glucose and plasma sodium levels than those in the moderate to severe handicap group. The combined group of brain damaged infants, (2 + 3), had lower Apgar scores at five minutes, umbilical cord arterial blood Standardized Base Excess (SBE), lower urinary output, and higher incidence of seizures and higher plasma potassium level than the group with normal development or those with mild handicap. Stepwise multiple logistic regression confirmed these.

LOE 4; E3; Fair; Supportive. Retrospective chart review; analysis of variance found association of lower blood glucose concentrations and early severe neurologic impairment.


STUDY OBJECTIVE: The purpose of this study was to determine the prevalence of hypoglycemia and describe the clinical variables associated with hypoglycemia in children receiving resuscitation care. METHODS: A cross-sectional study of consecutive children receiving resuscitation care in an emergency department was performed. Rapid glucose testing was prospectively established as one of the initial resuscitation steps, and clinical variables were obtained from a
ATPase activity and levels of lipid peroxidation products in hyperglycemic hypoxic animals were not significantly different and an increase in conjugated dienes and fluorescent compounds, markers of lipid peroxidation. In contrast, Na+,K(+) - external and internal carotid and subclavian arteries and the clamping of the left external and internal carotid arteries for 2h. The peritoneal injection of a 50% glucose solution (0.10 ml/15 g weight) 5 min before the induction of cerebral hypoxia was induced in groups 3 and 4 by reducing fraction of inspired oxygen for 60 min and was documented by a decrease in the ratio of phosphocreatine to inorganic phosphate as measured using 31P-nuclear magnetic resonance spectroscopy. Blood glucose concentration during hypoxia in hyperglycemic hypoxic animals was 20.7 +/- 1.2 mmol/L, compared with 10.3 +/- 1.7 mmol/L in untreated hypoxic piglets (p < 0.05). Peak lactate concentrations were not significantly different between the two hypoxic groups (8.4 +/- 2.8 mmol/L versus 7.8 +/- 1.6 mmol/L). In cerebral cortical membranes prepared from the untreated animals, cerebral tissue hypoxia caused a 25% reduction in Na+,K(+) -ATPase activity compared with normoxic controls and an increase in conjugated dienes and fluorescent compounds, markers of lipid peroxidation. In contrast, Na+,K(+) -ATPase activity and levels of lipid peroxidation products in hyperglycemic hypoxic animals were not significantly different from the values in control normoxic animals. (ABSTRACT TRUNCATED AT 250 WORDS)


To test the hypothesis that acute hyperglycemia reduces changes in cell membrane structure and function during cerebral hypoxia in the newborn, brain cell membrane Na+,K(+) -ATPase activity and levels of membrane lipid peroxidation products were measured in four groups of anesthetized, ventilated newborn piglets: normoglycemia/normoxia (control, group 1, n = 12), hyperglycemia/normoxia (group 2, n = 6), untreated hypoxia (group 3, n = 10), and hyperglycemia/hypoxia (group 4, n = 7). Hyperglycemia (blood glucose concentration 20 mmol/L) was induced using the glucose clamp technique. The hyperglycemic glucose clamp was maintained for 90 min before onset of hypoxia and throughout the period of hypoxia. Cerebral tissue hypoxia was induced in groups 3 and 4 by reducing fraction of inspired oxygen for 60 min and was documented by a decrease in the ratio of phosphocreatine to inorganic phosphate as measured using 31P-nuclear magnetic resonance spectroscopy. Blood glucose concentration during hypoxia in hyperglycemic hypoxic animals was 20.7 +/- 1.2 mmol/L, compared with 10.3 +/- 1.7 mmol/L in untreated hypoxic piglets (p < 0.05). Peak lactate concentrations were not significantly different between the two hypoxic groups (8.4 +/- 2.8 mmol/L versus 7.8 +/- 1.6 mmol/L). In cerebral cortical membranes prepared from the untreated animals, cerebral tissue hypoxia caused a 25% reduction in Na+,K(+) -ATPase activity compared with normoxic controls and an increase in conjugated dienes and fluorescent compounds, markers of lipid peroxidation. In contrast, Na+,K(+) -ATPase activity and levels of lipid peroxidation products in hyperglycemic hypoxic animals were not significantly different from the values in control normoxic animals. (ABSTRACT TRUNCATED AT 250 WORDS)

LOE 5; E1; Good; Supportive. Study with glucose pretreatment and controlled glucose concentration; pure hypoxia rather than hypoxia-ischemia; only looked at biochemical indices of injury, not neurologic or pathologic outcomes.


To examine the effects of hyperglycemia on a transient ischemia in the newborn brain, neuropathological and biochemical evaluations were performed. In 10-day-old rats, brain ischemia was induced by permanent occlusion of the right external and internal carotid and subclavian arteries and the clamping of the left external and internal carotid arteries for 2h. The peritoneal injection of a 50% glucose solution (0.10 ml/15 g weight) 5 min before the induction of brain ischemia increased the plasma glucose concentration to 20-25 mmol/l during ischemia. It preserved brain tissue glucose levels at 1h of ischemia in the glucose-treated group, while tissue glucose was exhausted in the saline-injected group. Tissue lactate concentrations increased slightly at the end of the ischemic insult (6.7 mmol/kg) in the saline-injected group and remarkably (18.7 mmol/kg) in the glucose-treated group. Two distinct forms of ischemic neuronal change were found in this study: ischemic cell change and reactive neuronal change. A quantitative neuropathological assessment indicated that hyperglycemia significantly reduced the volume of ischemic cell change in the neocortex from 85% to 33%, but not that of reactive neuronal change (from 5.5% to 2.4%). These results indicated that hyperglycemia attenuated ischemic cell change, but not reactive neuronal change, in the neonatal rat brain and suggested that it reduced ischemic cell change probably because of reserved brain glucose.

LOE 5; E1; Good; Supportive. Study in 10-day old rats; glucose administration before induction of ischemia reduced ischemic cell change.


BACKGROUND: Birth asphyxia contributes significantly to perinatal morbidity and mortality especially in resource poor countries. Although the Apgar score has been in use for over 50 years, the prevalence of low Apgar score and attendant risk factors and outcome have not been established in many sub-Saharan countries including Uganda. OBJECTIVE: To determine the prevalence of low Apgar score and establish immediate outcome and possible risk factors for poor

**Note:** The text is truncated at 250 words. Further details may be required to provide a complete understanding of the research.
outcome in babies with low Apgar score. SETTING: Labour wards, operating theatres and special baby care unit, Mulago Teaching and referral Hospital, Uganda. SUBJECTS: Babies delivered in Mulago Hospital between September and October 1999. Those with low Apgar scores, together with an equal number of babies with normal scores matched for sex as controls, were followed up for 48 hours. MEASUREMENTS: Clinical features, anthropometry, gestational age, oxygen saturation, blood glucose and autopsy of babies who died. MAIN OUTCOME MEASURES: Clinical improvement, death, complications such as HIE, RDS, aspiration pneumonia, hypoglycaemia, hypothermia, hypotension and hypoxaemia. RESULTS: The prevalence of low Apgar score at one and five minutes was 8.4% and 2.8% respectively. Adverse outcome was seen in 57.3% of cases: death in 12.1% and clinical complications in 45.2%. HIE occurred in 21.8%, hypoglycaemia in 12.9%, hypoglycaemia in 16.9% and aspiration pneumonia in 4.8%. Maternal factors significantly associated with low Apgar scores included primiparity, abnormal delivery, age and medical diseases during pregnancy, while birth injuries and cord accidents were the baby factors. Poor outcome was associated with birth injury, hypothermia, hypoglycaemia, hypotension, aspiration pneumonia, hypoxaemia and severe birth asphyxia. CONCLUSION: Even though the prevalence of low Apgar was only 8.4%, adverse outcomes associated with it were observed in more than half the patients. Therefore there is need to carefully evaluate and monitor babies with low Apgar scores immediately after birth.

LOE 3: E3; Good; supportive. Chart review of newborns with low Apgar scores; sex-matched controls with normal Apgars. Standardized data collection. Hypoglycemia more common in babies who died.


Episodes of hypoxia often occur in hypoglycemic newborns, but it is not known whether dysfunctions in cerebrovascular regulation contribute to brain injury incurred by these affected neonates. We tested the hypotheses that 1) perinatal hypoglycemia impairs cerebrovascular responses to hypoxia and 2) a reduced vascular smooth muscle sensitivity to adenosine accounts for this impairment. Responses of 25- to 50-mu m-diam pial arterioles were determined using the cranial window technique in isoflurane-anesthetized newborn piglets < 5 days of age. Hypoxia (arterial PO2 = 28 +/- 1 mmHg) caused a 47 +/- 5% increase (P = 0.0008) in arteriolar diameter, 89% of which could be blocked by prior superfusion of the window space with the preferential A2-adenosine receptor antagonist 3,7-dimethyl-1-propargylxanthine (DMPX; 50 microM). Insulin-induced hypoglycemia (blood glucose = 18 +/- 1 mg/dl without isoelectric electroencephalogram) caused a 31 +/- 5% increase (P = 0.002) in arteriolar diameter; however, no additional dilative response to hypoxia (arterial PO2 = 28 +/- 1 mmHg) could be elicited in these animals. Arteriolar dilation of 41 +/- 6% (P = 0.002) induced by superfusion of 20 microM adenosine under normoglycemic conditions was also completely abolished after the animals were rendered hypoglycemic. Unlike the response to hypoxia and adenosine, hypoglycemia only attenuated prostanoid-dependent dilations to hypercapnia (arterial PCO2 = 68 +/- 3 mmHg) by 55 +/- 9%. These results indicate that, in the newborn, hypoglycemia selectively abolishes hypoxic reactivity through an impairment in adenosine-mediated cerebrovascular dilation.

LOE 5; E1; Fair; Supportive. Animal study with pre-hypoxic manipulation of glucose; did not look at long-term outcomes. Results suggest that hypoglycemia could exacerbate hypoxic injury by blunting normal physiologic responses.


This study was done to determine the effects of hyperglycemia or hypoglycemia on brain cell membrane function and energy metabolism during the immediate reoxygenation-reperfusion period after hypoxia-ischemia (HI). Forty-five newborn piglets were divided randomly into four experimental groups: normoxia control (NC, n=9); HI/reoxygenation-reperfusion (RR) control (HC, n=11); HI/RR hyperglycemia (HE, n=12); and HI/RR hypoglycemia (HO, n=13) group. Animals were subjected to transient HI for 30 min followed by 2 h of RR. Cerebral HI was induced by temporary but complete occlusion of bilateral common carotid arteries with surgical clips and simultaneous breathing with 8% oxygen. Glucose was unregulated in HC group, and controlled by modified glucose clamp technique immediately after HI in HE (350 mg/dl) and HO (50 mg/dl) groups. During HI, heart rate, base deficit, glucose and lactate level in the blood and cerebral spinal fluid increased, and arterial pH, oxygen saturation and blood pressure decreased significantly in HC, HE and HO groups. During RR, these abnormalities returned to normal values, but lactic acidosis persisted especially in HO group. Cerebral Na(+),K(+)-ATPase activity decreased, and lipid peroxidation products increased significantly in HC group than in NC group, and these abnormalities were significantly aggravated in HE, but not in HO, group. Brain ATP and phosphocreatine levels in HE group were significantly reduced compared to the corresponding values in NC, HC and HO groups. In summary, hyperglycemia, but not hypoglycemia immediately after HI interfered with the recovery of brain cell membrane function and energy metabolism. These findings suggest that post-hypoxic-ischemic hyperglycemia is not beneficial and might even be harmful in neonatal hypoxic-ischemic encephalopathy.

LOE 5 E2; Good; Opposing. Animal study with pre-insult manipulation of glucose; did not consider neurologic or pathologic outcome, only biochemical indices of altered brain structure. Indices altered more with hypoglycemia than normoglycemia.

The effect of preasphyxia blood glucose concentration on postasphyxia (PA) cerebral hemodynamics was examined in 21 newborn lambs. Glucose was unregulated in one group (n = 7), and controlled throughout the study by glucose clamp in hyperglycemic (n = 7) and hypoglycemic (n = 7) groups. Cerebral blood flow, determined using radiolabelled microspheres, and arterial and sagittal sinus O2 contents were measured at control, 5 min, 1, 2, and 4 h after resuscitation from an asphyxial insult. Preasphyxia blood glucose were 6.48 +/- 0.55 mM (mean +/- SEM), 12.08 +/- 0.80, and 2.66 +/- 0.14 in the three study groups. In all three groups, 5 min PA cerebral blood flow was significantly increased from control. In the late period after asphyxia, the unregulated group had decreased cerebral blood flow compared with control, 53.2 +/- 3.8 mL100 g-1.min-1, mean +/- SEM, p < 0.01; 49.6 +/- 2.0, p < 0.005; 53.4 +/- 3.0, p < 0.01, at 1, 2, and 4 h PA, respectively, versus 85.7 +/- 6.9 at control, whereas both the hyper- and hypoglycemic groups did not differ significantly from control measurements. Cerebral oxygen consumption (CMRO2) was significantly decreased in all three groups 5 min PA and remained decreased in the late period after asphyxia in both the unregulated and hypoglycemic groups. In the unregulated group, CMRO2 was 191 +/- 14 microM.100 g-1.min-1, mean +/- SEM, p < 0.05; 200 +/- 4; and 181 +/- 10, p < 0.05 at 1, 2, and 4 h, respectively, PA versus 251 +/- 12 at control.

LOE 5; E1; Fair; Supportive. : Animal study with glucose pretreatment; did not look at overall neurologic or pathologic outcomes but suggests that hyperglycemia normalizes cerebral metabolism post-asphyxia.


OBJECTIVE: To determine the potential contribution of initial hypoglycemia to the development of neonatal brain injury in term infants with severe fetal acidemia. METHODS: A retrospective chart review was conducted of 185 term infants who were admitted to the neonatal intensive care unit between January 1993 and December 2002 with an umbilical arterial pH <7.00. Short-term neurologic outcome measures include death as a consequence of severe encephalopathy and evidence of moderate to severe encephalopathy with or without seizures. Hypoglycemia was defined as an initial blood glucose < or =40 mg/dL. RESULTS: Forty-one (22%) infants developed an abnormal neurologic outcome, including 14 (34%) with severe neonatal hypoxic ischemic encephalopathy who died, 24 (59%) with moderate to severe hypoxic ischemic encephalopathy, and 3 (7%) with seizures. Twenty-seven (14.5%) of the 185 infants had an initial blood sugar < or =40 mg/dL. Fifteen (56%) of 27 infants with a blood sugar < or =40 mg/dL versus 26 (16%) of 158 infants with a blood sugar >40 mg/dL had an abnormal neurologic outcome (odds ratio [OR]: 6.3; 95% confidence interval [CI]: 2.6-15.3). Infants with abnormal outcomes and a blood sugar < or =40 mg/dL versus >40 mg/dL had a higher pH (6.86 +/- 0.07 vs 6.75 +/- 0.09), a lesser base deficit (-19 +/- 4 vs -23.8 +/- 4 mEq/L), and lower mean arterial blood pressure (34 +/- 10 vs 45 +/- 14 mm Hg), respectively. There was no difference between groups in the proportion of infants who required cardiopulmonary resuscitation (7 [46%] vs 15 [57%]) and those with a 5-minute Apgar score <5 (11 [73%] vs 22 [85%]). By multivariate logistic analysis, 4 variables were significantly associated with abnormal outcome: initial blood glucose < or =40 mg/dL versus >40 mg/dL (OR: 18.5; 95% CI: 3.1-111.9), cord arterial pH < or =6.90 versus >6.90 (OR: 9.8; 95% CI: 2.1-44.7), a 5-minute Apgar score < or =5 versus >5 (OR: 6.4; 95% CI: 1.7-24.5), and the requirement for intubation with or without cardiopulmonary resuscitation versus neither (OR: 4.7; 95% CI: 1.2-17.9). CONCLUSION: Initial hypoglycemia is an important risk factor for perinatal brain injury, particularly in depressed term infants who require resuscitation and have severe fetal acidemia. It remains unclear, however, whether earlier detection of hypoglycemia, such as in the delivery room, in this population could modify subsequent neurologic outcome.

LOE 4; Fair; E3; Supportive. Review of outcomes in newborns with severe acidemia at delivery and analysis of risk factors associated with poor outcome. Blood glucose < or =40 mg/dL associated with adverse outcome.


Brain glucose concentration during and after hypoxia-ischemia may be one of the variables affecting outcome of asphyxial insults. Glucose given before global ischemic forebrain injury to adult rats increases morphologic brain damage, and postischemic insulin administration reduces selective neuronal necrosis and cortical infarction. Because glucose infusions are routinely used in the clinical management of perinatal asphyxia, we evaluated the role of glucose administration after ischemic neuronal damage to neonatal rat brain. Sprague-Dawley rat pups (postnatal day 7) were subjected to left common carotid artery ligation followed by 2.5 h of 8% oxygen (Levine procedure). The experimental group was subdivided so that pups received either systemic injections of glucose or saline immediately after the hypoxic insult. Animals were killed on postnatal day 12 and brain areas of ipsi- and contralateral cortex and caudate were calculated from camera lucida tracings. There was no significant difference in size of brain infarction between posts ischemic glucose-treated and post-ischemic saline-treated pups. However, hypoxic-ischemic brains did show more severe neuronal damage when hyperglycemia was induced after asphyxia. Because post-ischemic hyperglycemia does
not attenuate and may exacerbate injury, we recommend careful monitoring of blood glucose so that hyperglycemia does not occur during resuscitation of asphyxiated infants.

LOE 5; E2; Good; Opposing. Glucose treatment post-insult; no regulation of glucose concentration. Contradicts Hattori and Wasterlain, with suggestion that there may be an increase in neuronal injury after glucose administration.


Recently, we observed that pre-treatment of neonatal rats with dexamethasone prevents brain damage associated with cerebral hypoxia-ischemia (unilateral carotid occlusion + 3 h hypoxia). Presently, we investigate whether hyperglycemia or an induction of endogenous free radical scavengers explains dexamethasone's neuroprotective effect. Pathological damage was examined in rats maintained hypoglycemic during hypoxia-ischemia by the repeated administration of 10% glucose (10 ml/kg, i.p.) at 0, 1, 2 and 3 h of hypoxia (n = 14) and this damage was compared to that in control (n = 15) or dexamethasone (0.1 mg/kg, i.p., n = 15) treated animals. Despite similar elevations in blood glucose at the end of hypoxia, glucose treated animals had greater damage than dexamethasone treated animals and both of these groups had less damage than controls (volumes of damage of approx. 30.9 +/- 10, 3.4 +/- 2.3 and 60.4 +/- 7.1% of the hemisphere, respectively; P < 0.0001). Anti-oxidant enzyme activities were measured within brains of animals treated with dexamethasone or vehicle (n = 44). Activities of the enzymes catalase, glutathione peroxidase and CuZn- or Mn-superoxide dismutase were similar in both treatment groups, with or without exposure to hypoxia-ischemia. Thus, an induction of antioxidant enzymes does not explain dexamethasone's effects whereas the relative hyperglycemia associated with glucocorticoid treatment may contribute partially. Neither account fully for dexamethasone's protective effect suggesting an additional glucocorticoid mediated mechanism must be involved.

LOE 5; E1; Good; Supportive. Animal study with glucose administration before and during insult. Not designed to examine the effect of glucose on hypoxic-ischemic brain injury, but did show partial protective effect of hyperglycemia.


The cerebral metabolic responses to perinatal hypoglycemia and anoxia were studied in newborn rats given regular insulin (30 units per kilogram of body weight). Animals were observed for up to 2 hours with no apparent ill effects in spite of blood glucose concentrations of 0.75 mmol per liter. When exposed to 100% nitrogen at 37 degrees C, hypoglycemic animals survived only one-tenth as long as littermate controls with normal blood glucose levels (4.7 mmol/L). Pretreatment of hypoglycemic rats with glucose (10 mmol/kg) 10 and 30 minutes prior to nitrogen exposure nearly completely reversed the anoxic vulnerability. Hypoglycemia led to progressive reductions in cerebral glycogen and glucose; however, only glucose reverted to normal levels 20 minutes after systemic glucose administration. The glycolytic intermediates glucose 6-phosphate and lactate were also lower during hypoglycemia. Brain glucose levels below 0.1 mmol per kilogram were associated with a disrupted cerebral energy state, reflected by declines in phosphocreatine (33%) and adenosine triphosphate (ATP) (10%). Cerebral energy utilization (metabolic rate) was minimally reduced (-7.2%) by hypoglycemia and returned to the control value (2.36 mmol approximately P/kg/min) with glucose treatment. The cerebral energy reserves ATP, adenosine diphosphate, and phosphocreatine declined more rapidly and to a lower level in hypoglycemic rats subjected to 2 1/2 minutes of anoxia than in normoglycemic animals rendered similarly hypoxic. The findings suggest that decreased anoxic resistance of hypoglycemic newborn rats is not primarily a function of reduced brain glycogen or altered cerebral metabolic rate. The presence of endogenous cerebral glucose stores combined with continued circulating glucose (cerebrovascular perfusion) appear to be critical factors for maintaining perinatal hypoxic survival.

LOE 5; E1; Good; Supporting. Animal study with glucose pretreatment. Blood glucose concentrations in the hypoglycemia group were not regulated and varied considerably, making it impossible to determine the blood glucose level associated with decreased survival.


The cerebral metabolic responses to perinatal hypoglycemia (blood glucose less than or equal to 1 mmol/l) combined with asphyxia were studied in paralyzed, lightly anesthetized newborn dogs. No major differences in heart rate, blood pressure or arterial acid-base balance between control and hypoglycemic animals occurred either prior to or during asphyxia. The electroencephalogram, unaltered by hypoglycemia alone, became isoelectric at the same intervals in both groups following respiratory arrest. Intravenous carbon black infusion at 5 min of asphyxia demonstrated no relationship between blood glucose level and cerebral perfusion (p > 0.05), whereas a positive correlation did exist between systemic blood pressure and cerebral perfusion (p < 0.01). During asphyxia, anaerobic glycolysis in brain was less enhanced in hypoglycemic dogs, resulting in a more rapid exhaustion of high-energy phosphate reserves (phosphocreatine, ATP and ADP). Thus, the cerebral metabolic responses to asphyxia superimposed upon hypoglycemia were the direct consequence of insufficient cerebral glucose stores coupled with deficient circulating glucose to brain. These metabolic disturbances were no more the result of cerebral ischemia than that which occurs during asphyxia alone. The findings
also suggest that systemic physiological monitoring may be an inadequate means of appraising cerebral homeostasis during combined hypoglycemia and hypoxia.

LOE 5; E1; Good; Supportive. Study in newborn dogs; hypoglycemia in combination with asphyxia associated with more rapid depletion of cerebral high energy phosphate levels.


Unlike adults, hyperglycemia with circulating glucose concentrations of 25-35 mM/L protects the immature brain from hypoxic-ischemic damage. To ascertain the effect of hyperglycemia on cerebral oxidative metabolism during the course of hypoxia-ischemia, 7-day postnatal rats underwent unilateral common carotid artery ligation followed by exposure to 8% O2 for 2 h at 37 degrees C. Experimental animals received 0.2 cc s.c. 50% glucose at the onset of hypoxia-ischemia, and 0.15 cc 25% glucose 1 h later to maintain blood glucose concentrations at 20-25 mM/L for 2 h. Control rat pups received equivalent concentrations or volumes of either mannitol or 1 N saline at the same intervals. The cerebral metabolic rate for glucose (CMRglc) increased from 7.1 (control) to 20.2 mumol 100 g-1 min-1 in hyperglycemic rats during the first hour of hypoxia-ischemia, 79 and 35% greater than the rates for saline-and mannitol-injected animals at the same interval, respectively (p < 0.01). Brain intracellular glucose concentrations were 5.2 and 3.0 mM/kg in the hyperglycemic rat pups at 1 and 2 h of hypoxia-ischemia, respectively; glucose levels were near negligible in mannitol- and saline-treated animals at the same intervals. Brain intracellular lactate concentrations averaged 13.4 and 23.3 mM/kg in hyperglycemic animals at 1 and 2 h of hypoxia-ischemia, respectively, more than twice the concentrations estimated for the saline- and mannitol-treated littermates. Phosphocreatine (PCr) and ATP decreased in all three experimental groups, but were preserved to the greatest extent in hyperglycemic animals. Results indicate that anaerobic glycolytic flux is increased to a greater extent in hyperglycemic immature rats than in normoglycemic littermates subjected to cerebral hypoxia-ischemia, and that the enhanced glycolysis leads to greater intracellular lactate accumulation. Despite cerebral lactosis, energy reserves were better preserved in hyperglycemic animals than in saline-treated controls, thus accounting for the greater resistance of hyperglycemic animals to hypoxic-ischemic brain damage.

LOE 5; E1&2; Good; Supportive. Study done in & day old rats; cerebral energy reserves better preserved during hypoxia-ischemia in hyperglycemic rats compared to controls.


Seven-day postnatal rats were rendered hyperglycemic by the SC injection of 50% glucose, following which they were exposed to hypoxia with 8% oxygen. The glucose-treated animals survived more than twice as long as saline-treated littermates. Other hyperglycemic and control rat pups were subjected to hypoxia-ischemia by unilateral common carotid artery occlusion combined with 2 hours of hypoxia. Neuropathologic analysis of recovered animals at 30 days of age showed that the brains of the glucose-treated animals were no more damaged than those of the saline controls (p greater than 0.05). The finding indicates that, unlike adults, glucose supplementation and its associated hyperglycemia in the immature rat does not increase the extent of hypoxic-ischemic brain damage.

LOE 5; E1; Good; Neutral. Animal study with glucose pretreatment. No deleterious effects of hyperglycemia during hypoxia-ischemia, in direct contrast to adult data. Glucose concentrations varied in experimental animals; 7-day rat model may not be equivalent to perinatal asphyxia.


OBJECTIVE: We evaluated retrospectively plasma glucose levels and the degree of hypoglycemia, hyperglycemia, and glucose variability in a PICU and then assessed their association with hospital length of stay and mortality rates.

METHODS: Electronic medical records at the Packard Children's Hospital at Stanford University were reviewed retrospectively for all PICU admissions between March 1, 2003, and March 31, 2004. Patients with a known diagnosis of diabetes mellitus were excluded. The prevalence of hyperglycemia was defined with cutoff values of 110, 150, and 200 mg/dL. Hypoglycemia was defined as < or = 65 mg/dL. Glucose variability was assessed with a calculated glucose variability index. RESULTS: In 13 months, 1094 eligible admissions generated 18865 glucose values (median: 107 mg/dL; range: 13-1839 mg/dL). Patients in the highest maximal glucose quintile had a significantly longer median PICU length of stay, compared with those in the lowest quintile (7.5 days vs 1 day). Mortality rates increased as patients' maximal glucose levels increased, reaching 15.2% among patients with the greatest degree of hyperglycemia. Hypoglycemia was also prevalent, with 18.6% of patients (182 of 980 patients) having minimal glucose levels of < or = 65 mg/dL. There was an increased median PICU length of stay (9.5 days vs 1 day) associated with glucose values in the lowest minimal quintile, compared with those in the highest quintile. Hypoglycemia was correlated with mortality rates; 16.5% of patients with glucose levels of < or = 65 mg/dL died. Glucose variability also was associated with increased length of stay and mortality rates. In multivariate logistic regression analyses, glucose variability, taken with hyperglycemia and hypoglycemia, showed the strongest association with mortality rates. CONCLUSIONS:
Hyperglycemia and hypoglycemia were prevalent in the PICU. Hypoglycemia, hyperglycemia, and, in particular, increased glucose variability were associated with increased morbidity (length of stay) and mortality rates.

LOE 5; E3; Poor; Supportive. Review of medical records of patients admitted to PICU. Glucose measurements made based on clinical indications; not standardized. High degree of glucose variability more closely associated with adverse outcome than either hypoglycemia or hyperglycemia; suggests physiologic instability, not glucose concentration, was responsible for the differences in outcome.


Experiments in adult animals have indicated that hyperglycemia accentuates whereas hypoglycemia ameliorates hypoxic-ischemic brain damage. To determine whether hypoglycemia is protective or deleterious to the perinatal brain subjected to hypoxia-ischemia, 7-d postnatal rats were rendered hypoglycemic either by receiving an s.c. injection of insulin or fasting for 12 h. All rat pups underwent unilateral common carotid artery ligation followed by exposure to 8% oxygen-balance nitrogen at 37 degrees C for 2 h. Control animals (no insulin or fasting) received s.c. injections of normal saline. Mean blood glucose concentrations were 5.4 +/- 0.1, 4.3 +/- 0.2, and 3.4 +/- 0.1 mmol/L for control, insulin, and fasted animals, respectively. Blood beta-hydroxybutyrate concentrations were identical (0.5 +/- 0.1 mmol/L) for control and insulin-treated animals, but more than doubled in concentration in the fasted animals (p less than 0.001). Mortality rates during hypoxia-ischemia were higher in the insulin-treated animals (30%) than in either the fasted (4%) or control (0%) animals (p less than 0.05). Fasted animals showed a significant reduction in hypoxic-ischemic brain damage as compared with either the insulin-treated or control animals. Insulin-treated animals were not significantly different from controls. The findings indicate that 1) insulin induced hypoglycemia does not provide a protective effect on perinatal hypoxic-ischemic brain damage, as in adults; and 2) fasting adequate to produce hypoglycemia and ketonemia improved neuropathologic outcome.

LOE 5; E1; Good; Neutral. Animal study with pre-insult manipulation of glucose, but actual blood glucose concentration not specifically regulated. Results suggests that hyperinsulinemic hypoglycemia (as may occur post-asphyxia) increases injury due to suppression of ketone production.


Aim: To study the association between intellectual development and blood sugar in newborns with hypoxic ischemic encephalopathy (HIE), which can cause brain hypoevolutionism, cerebral palsy, mental retardation, epilepsy and other sequelae. Methods: Fifty-six HIE newborns meeting the inclusive criteria were enrolled from the impatient of Liaoning People’s Hospital from January 1999 to December 2002, including 30 males and 26 females. 1 After admission, all the HIE newborns had an examination in blood sugar every 4 hours to regulate blood sugar level until it recovered to normal. Meanwhile, CT and electroencephalograph (EEG) examinations were conducted. 2 Infant intellectual development measure scale designed by China Children Development Center was used to assess the intellectual development level of infant at 3 and 6 months of age. Intellectual development level was expressed by development index. Infant with a score < 50 was considered as having dysnoesia. The bigger the index was, the better the intellectual development was. 3 Gesell development scale was used to assess the intellectual development of infants at 12-24 months of age, and then to study the occurrence of sequelae. Gesell development scale measures four areas: motricity, adaptation, speech and sociability. Developmental quotient can be calculated according to the score on scale and actual age. Developmental quotient= Mature age/actual age x 100%. Total score is the average score on motricity, adaptation, speech and sociability. If total score was less than 85, it was indicated that some body injuries exist, maybe dropping behind seriously. A higher score indicated a better intellectual development. Results: Fifty-six newborns were enrolled in the study, but only 41 ones were involved in the result analysis. Other 15 included 7 cases of death and 8 cases discharged according to the demand of their parents. 1 Among infants at 3 and 6 months of age, intellectual developmental index was higher in infants with normal blood sugar than those with abnormal blood sugar (94.89±8.73, 95.63±10.75; 6.58±13.95, 87.68±12.69, t=2.203, 2.083, P < 0.05). 2 Total score on Gesell development scale was higher in normal blood sugar group than in abnormal blood sugar group (102.84±8.66, 95.42±7.24, t=2.866, P < 0.01). 3 Cases of sequelae were more in abnormal blood sugar group than in normal blood sugar group [7 cases (35%), 2 cases (10%), χ²=3.881, P < 0.05]. 4 Brain CT and EEG: Of the 24 cases of normal blood sugar, there were 6 cases (25%) of intracranial hemorrhage showed by CT, and 5 cases (21%) of abnormal EEG; Of the 32 cases of abnormal blood sugar, there were 21 cases (66%) of intracranial hemorrhage showed by CT, and 20 cases (62%) of abnormal EEG. Conclusion: Infants with abnormal blood sugar are more likely to have dysnoesia, sequelae, and abnormal CT and EEG than those with normal blood sugar. Therefore, it is beneficial to decrease brain functional injury and improve intellectual development through maintaining blood sugar at a normal level in HIE infants.

LOE 4; E3; Good; Supportive. Prospective follow-up of babies with HIE; no normal controls. Only study with relatively long-term follow-up (to 12-24 months) and neurodevelopmental testing.