"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)?"

**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” 9 hits

Web of Knowledge (ISI): (“hypoglycemia or hyperglycemia”) AND (“asphyxia or hypoxia-ischemia”) AND (“newborn or “neonat*”) 15 unique hits

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

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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

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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### Level of evidence

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

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 level
# Evidence Opposing Clinical Question

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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
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 with 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 hyperglycemia 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 (Laptop 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).

**Acknowledgements:** None
Citation List


LOE 5; E3; Poor; Supportive. Retrospective analysis of data from animal study that was not specifically designed to look at effects of glucose concentration. Low blood glucose levels associated with poor short-term neurologic outcomes, but glucose concentrations were not specifically regulated.


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


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.


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.


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.


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


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.


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.

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


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.


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.


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


LOE 5; E3; Poor; Supportive. Retrospective study of frequency of hypoglycemia in children requiring “resuscitative care” in the emergency room. Timing of blood sampling for glucose level varied, as did diagnoses.


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.


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


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.


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.


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.

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.


LOE 4; Fair; E3; Supportive. Review of outcomes in newborns with severe acidaemia at delivery and analysis of risk factors associated with poor outcome. Blood glucose ≤40 mg/dl associated with adverse outcome.


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.


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.


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.


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


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.


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.


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.

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.


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.