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

**Worksheet author(s)**

| Jeffrey M Perlman | Date Submitted for review: 1/29/09 |

Your worksheet tracking number is NRP-019B

**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 (O)? (outcome includes avoidance of hypoglycemia, long-term neurologic morbidity

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

State if this is a proposed new topic or revision of existing worksheet: 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).**

Since this was a modified revision and the prior search was through December 2004, this search was conducted from January 05 through January 09

Key words used included hypoglycemia, resuscitation, delivery room, newborn, asphyxia, brain injury,

Ovid Medline – “Mesh” hypoglycemia + resuscitation 28 hits (0 used), hypoglycemia + delivery room – 9 hits (2 used) glucose + delivery room 6 hits (0 used), hypoglycemia + hypoxia-ischemic brain injury 24 hits (0 used) hypoglycemia + asphyxia 18 hits (0 used), asphyxia, hypoxic-ischemia, brain injury, newborn,

Embase “Mesh” hypoglycemia + resuscitation 20 hits (0 used), hypoglycemia + delivery room – 9 hits (1 used) glucose + delivery room 7 hits (1 used), hypoglycemia + hypoxia-ischemic brain injury 50 hits (1 used) hypoglycemia + asphyxia 62 hits (0 used),

Cochrane library- terms hypoglycemia, newborn - 0 hits

Review articles 2

Endnote library terms hypoglycemia 17 hits

**State inclusion and exclusion criteria**

Reviews were confined to newborn neonatal clinical studies. Since 2005 two articles were identified – both were tangential to the question asked. Non English abstracts were reviewed where found. Thus this worksheet includes 18 articles

Excluded No animal studies and case reports

**Number of articles/sources meeting criteria for further review:**

Two articles
### Summary of evidence

#### Evidence Supporting 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 (O)?

<table>
<thead>
<tr>
<th>Good</th>
<th>Salhab, 2004 E</th>
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<tbody>
<tr>
<td>Chang 1999 D</td>
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<td>Park 2001 D</td>
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<td>Voorhies, 1986 D</td>
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<td>Laptook 1992 E</td>
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<td>Rosenberg 1990 E</td>
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<td>Mcgowan 1995 E</td>
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<td>Vannucci 1996 E</td>
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<td>Yager, 1992</td>
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<th>Fair</th>
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<td>Brambrink, 1999 E</td>
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<td>Burns 2008 E</td>
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<td>Silva 2008 E</td>
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<table>
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<tr>
<th>Poor</th>
<th>Ondo-Onawa 2003 E,</th>
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<td>Lin 1996 E</td>
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<td>Mir 1989 E</td>
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<table>
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<tr>
<th>Level of evidence</th>
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<tbody>
<tr>
<td>A = Return of spontaneous circulation</td>
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<tr>
<td>B = Survival of event</td>
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<tr>
<td>C = Survival to hospital discharge</td>
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<tr>
<td>D = Intact neurological survival</td>
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<tr>
<td>E = Other endpoint</td>
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<td>Italics = Animal studies</td>
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</table>
Evidence Neutral to 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 (O)?

<table>
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<th>Good</th>
<th>Fair</th>
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<th>LeBlanc, 1994 D Sheldon 1992 E</th>
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Evidence Opposing 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 (O)?

<table>
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<th>Good</th>
<th>Fair</th>
<th>Poor</th>
<th>Hattori, 1990E</th>
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</table>

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*
REVIEWER'S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

The impact of glucose on brain injury at the time of hypoxia-ischemia differs in neonates as opposed to adults. Thus during or after hypoxia-ischemia, immature brain tissue appears to be specifically vulnerable to hypoglycemia as shown in neonatal animals (Vannucci (LOE 5), Brambrink(LOE 5)). Moreover the method of inducing hypoglycemia may influence outcome. Animals subjected to hypoglycemia induced by insulin versus fasting had greater mortality and a tendency towards enhanced neuropathologic morbidity (Yager (LOE 5)). However a second study utilizing this model failed to demonstrate this differential effect of insulin on outcome (Chang (LOE 5)). There are four retrospective human studies suggesting a deleterious role of hypoglycemia with asphyxia and subsequent brain injury (Salhab (LOE 4), Lin et al (LOE 5) Mir (LOE 4),Ido-Onawa (LOE 4)). Indeed in the study of Salhab, there was an 18-fold increased likelihood for neonatal encephalopathy in infants with a blood glucose <40 mg/dL requiring resuscitation as compared to those with a blood glucose > 40mg/dL. Finally a neuroimaging study indicates a specific vulnerability of brain i.e. parietal-occipital deep white and gray matter with hypoglycemia. The MRI changes were associated with an abnormal outcome (Burns 2008, LOE 5).

In studies of newborn animals, who were preloaded with glucose or saline and then subjected to hypoxia, the glucose loaded animals survived more than twice as long as their control littermates and neuropathologic examination revealed comparable changes in both groups (Voorheis 1986 (LOE 5)). Glucose loading resulted in increased glucose transport into the brain but not with enhanced glucose utilization or lactate accumulation with hypoxia-ischemia compared with that of animals subjected to hypoxia-ischemia alone (Vannucci, 1996(LOE 5)). Low activity of the glucose phosphorylating enzyme, which is rate limiting for glucose utilization, accounts for the similar rates of glucose consumption in hyperglycemic and normoglycemic immature rats (Booth, 1980). Thus the animal studies would suggest that hypoglycemia during hypoxia-ischemia is deleterious to brain whereas hyperglycemia maybe protective.

Additional studies indicate that the influence of glucose loading appears to be time related. Thus when given immediately following hypoxia-ischemia there is some benefit (neuronal survival) that is lost when the infusion of glucose is delayed by at least one hour (Shelton (LOE 5), Le Blanc (LOE 5), Hattori et al (LOE 5)) One study indicates lower higher energy phosphate compounds as well as increased production of free radicals (Park (LOE 5)) while three studies utilizing metabolic end points indicate preservation of CMRO2 and ATP when glucose is maintained at high levels following ischemia (Laptook, Vannucci, Rosenberg (LOE 5)).

There are no studies in the neonate that have addressed the question of whether early supplemental glucose during and/or following delivery room resuscitation will and/or can improve outcome.

Based on the experimental data, and to a lesser extent on the clinical and neuroimaging data, the recommendation following the intensive resuscitation of the newborn infant is to avoid both low and high blood glucose concentrations. However the optimal glucose concentration to minimize brain injury cannot be defined based on available data.

Acknowledgements:
### Citation List

<table>
<thead>
<tr>
<th>Citation Marker</th>
<th>Full Citation*</th>
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<tbody>
<tr>
<td></td>
<td>Vannucci RC, Nardis EE, Vannucci SJ. Cerebral metabolism during hypoglycemia and asphyxia in</td>
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<tr>
<td>Reference</td>
<td>Description</td>
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<td>{Yager, 1992 #52}</td>
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</table>
Hypoglycemia


Critique: Non randomized study, outcome was related to the neurologic examination at 24 hours. No analysis with regard to the neuropathologic findings at 4 days was provided.


Comments. Observations linking hypoglycemia, MRI changes and adverse outcome

Level of Evidence 5
Quality fair
Evidence - supportive


Critique: Different levels of glucose utilized as gut off points-i.e. 60mg/dl for fasting and 35mg/dl for insulin induced hypoglycemia. No neuropathological end points provided.

Level of Evidence 5
Quality Good
Evidence - supportive


Critique : Retrospective study. The majority of infants were excluded from the data analysis. Asphyxia not defined –extent of delivery room resuscitation not provided. Hypoglycemia not defined. “Hypoglycemia” was the lowest glucose in the first 24 hours. In the logistic model the negative influence of hypoglycemia was noted with withdrawal of care but not for all infants with abnormal neurologic outcome. Data are difficult to analyze as presented.

Level of Evidence 5
Quality poor
Evidence - supportive


Critique: Poor definition of asphyxia. The definition of hypoglycemia not provided. The data analysis is inadequate. Largely preterm infants. Overall very poor study – not included in the grid

Level of Evidence 5-
Quality Poor


Critique No definition of hypoglycemia provided. The contribution of hypoglycemia to adverse outcome as determined by logistic modeling not provided.

Level of Evidence 5
Quality fair to poor
Evidence - supportive

Critique: Retrospective study in a high risk newborn population for brain injury. Hypoglycemia defined as a blood sugar ≤ 40mg/dl conferred an 18 fold increased risk for brain injury particularly in the context of intensive resuscitation. It remains unclear whether the hypoglycemia is a bi-product of in utero hypoxia-ischemia or whether it directly contributed to the injury.

Level of Evidence: 4
Quality: Good
Evidence: Supportive study


Conclusions: Although metabolic acidemia is significantly associated with hypotonia at the time of birth, the majority of neonates with hypotonia and depression or seizures do not have objective evidence of asphyxia as measured by a cord gas at the time of delivery.
Comment: Although not the primary intent of the manuscript, in the analysis there was an association between hypoglycemia and neonatal hypotonia.

Level of Evidence: 4
Quality: Fair
Evidence: Supportive study


Critique: Metabolic end points with no neuropathologic data.
Level of Evidence 5
Quality fair
Evidence – supportive


Critique: Non randomized study. Predefined end point not provided. Use of the preweaning rat model has been criticized because of the animal’s limited ability to metabolize glucose. Animals were not hypoglycemic using usual definition. Despite limitations, the study highlights the complex issues related to low blood sugar and brain injury with hypoxia-ischemia.

Level of Evidence 5
Quality Good –fair
Evidence - supportive

Hyperglycemia


Critique: Sample size calculation not provided. Not blinded. Rat model. Early effect of glucose observed, but no effect noted when glucose infusion was delayed (i.e. given at one hour).
Level of Evidence 5
Quality Fair
Evidence Neutral


Critique: Protective effect of increased glucose in terms of ATP preservation but no neuropathologic data.
Level of Evidence 5
Quality Fair
Evidence - supportive

Critique- good experimental design and in theory powered to detect a 10% difference in adverse pathologic outcome. Piglet model has a glucose metabolism similar to the human.

Level of Evidence 5
Quality Good
Evidence - Neutral


Level of Evidence 5
Quality Good
Evidence - supportive


Critique:  Non randomized, small numbers and no measurement of glucose levels. However rhesus monkey model that is perhaps closest to the human situation.

Level of Evidence 5
Quality Good to Fair
Evidence - Opposing


Critique:  The sample was not powered to detect a particular adverse outcome. Hypoglycemia was defined as a blood glucose of 50mg/dl- a value higher than is commonly used to define the condition.

Level of Evidence 5
Quality Fair
Evidence- Supportive


Critique: Large animal model (probably good). Unfortunately no neuropathologic data provided

Level of Evidence 5
Quality Good
Evidence - supportive


Critique:  Rat model. Sample size calculations not provided. Focal model as opposed to a global model of bilateral carotid occlusion. Some of the discrepancies in the studies may be related to the timing of the insult as it relates to the ontogeny of receptors. Thus from days 1-8, 85% of rat hippocampal neurons exhibit NMDA regulated spontaneous depolarization potentials whereas in rats 9 to 12 days of age it decreases to 50%.

Level of Evidence 5
Quality - Good to Fair
Evidence - Supportive

Critique: Rat pup model. Non randomized. Power analysis for sample size not provided.
Level of Evidence 5
Quality – Good
Evidence - supportive


Critique – Large model – differential adverse of hyperglycemia within brain.
Level of Evidence 5
Quality – Good
Evidence - supportive


Critique- Sample size power analysis not provided. Not blinded. Rat model

Level of Evidence 5
Quality Fair
Evidence - Supportive

**Selected Background Information**


