

WORKSHEET for PROPOSED Evidence-Based GUIDELINE RECOMMENDATIONS

Worksheet Author:	Taskforce/Subcommittee: __BLS __ACLS x PEDS __ID __PROAD _x_Other: NRP
Author's Home Resuscitation Council: _x_AHA __ANZCOR __CLAR __ERC __HSFC __HSFC __RCSA __IAHF __Other:	Date Submitted to Subcommittee: 11/08/04

STEP 1: STATE THE PROPOSAL. State if this is a proposed new guideline; revision to current guideline; or deletion of current guideline.

Existing guideline, practice or training activity, or new guideline: Revision to current guideline

Check the blood glucose level during stabilization after resuscitation

Step 1A: Refine the question; state the question as a positive (or negative) hypothesis. State proposed guideline recommendation as a specific, positive hypothesis. Use single sentence if possible. Include type of patients; setting (in-/out-of-hospital); specific interventions (dose, route); specific outcomes (ROSC vs. hospital discharge).

Serum glucose levels should be maintained within a normal range following intensive resuscitation in the term infant to minimize the potential risk for brain injury

Step 1B: Gather the Evidence; define your search strategy. Describe search results; describe best sources for evidence.

Key words used included MeSH words included the following:

hypoglycemia, hyperglycemia, glucose, neonatal brain injury, asphyxia, hypoxic-ischemia, brain injury, newborn, animal, swine

Embase Hypoglycemia+ newborn + hypoxia-ischemia – 11 hits- 8 used, hypoglycemia +newborn + brain injury – 46 hits- 5 used, animal + brain injury + hyper/hypoglycemia - 135 hits - 8 used, swine + hyper/hypoglycemia + brain injury – 24 hits-4 used

Medline – Hypo/hyperglycemia+ newborn + hypoxia-ischemia – 33 hits- 14 used, animal + hypoxia-ischemia+ hyper/hypoglycemia + newborn - 9 hits - 5 used

List electronic databases searched (at least AHA EndNote 7 Master library [<http://ecc.heart.org/>], Cochrane database for systematic reviews and Central Register of Controlled Trials [<http://www.cochrane.org/>], MEDLINE [<http://www.ncbi.nlm.nih.gov/PubMed/>], and Embase), and hand searches of journals, review articles, and books.

Medline(Pub Med), Embase, Cochrane Systemic reviews, ECC endnote library, review of references

- State major criteria you used to limit your search; state inclusion or exclusion criteria (e.g., only human studies with control group? no animal studies? N subjects > minimal number? type of methodology? peer-reviewed manuscripts only? no abstract-only studies?)

No abstracts or adult clinical and experimental studies were reviewed. Reviews were confined to newborn animal studies as well as neonatal clinical studies. There were four clinical neonatal studies identified that related in part to this specific question.

- Number of articles/sources meeting criteria for further review: Create a citation marker for each study (use the author initials and date or Arabic numeral, e.g., "Cummins-1"). If possible, please supply file of best references; EndNote 6+ required as reference manager using the ECC reference library.

The search yielded 218 hits. 18 papers are cited in this worksheet. Sixteen perinatal experimental studies and four neonatal clinical studies were identified and three are included in the evidence grid sheet-one was of a poor quality

STEP 2: ASSESS THE/QUALITY OF EACH STUDY

Step 2A: Determine the Level of Evidence. For each article/source from step 1, assign a level of evidence—based on study design and methodology.

**Level of
Evidence**

Definitions

(See manuscript for full details)

Level 1

Level 2

Level 3

Level 4 **Ondoa-Onawa 2003, Salhab, 2004**

Level 5 **Lin 1996,**

Level 6 Sheldon 1992, Park 2001, Laptook, 1992, LeBlanc 1994, Vannucci 1996, Vannucci, 1996 Rosenberg 1990, Voorhies 1986, Hattori 1990, Myers RE1977 , McGowan 1995, Vannucci1980, Yager1992, Chang 1999, Brambrink 1999,

Level 7
Level 8

Step 2B: Critically assess each article/source in terms of research design and methods.

Was the study well executed? Suggested criteria appear in the table below. Assess design and methods and provide an overall rating. Ratings apply within each Level; a Level 1 study can be excellent or poor as a clinical trial, just as a Level 6 study could be excellent or poor as an animal study. Where applicable, please use a superscripted code (shown below) to categorize the primary endpoint of each study. For more detailed explanations please see attached assessment form.

Component of Study and Rating	Excellent	Good	Fair	Poor	Unsatisfactory
Design & Methods	Highly appropriate sample or model, randomized, proper controls AND Outstanding accuracy, precision, and data collection in its class	Highly appropriate sample or model, randomized, proper controls OR Outstanding accuracy, precision, and data collection in its class	Adequate, design, but possibly biased OR Adequate under the circumstances	<i>Small or clearly biased population or model</i> OR <i>Weakly defensible in its class, limited data or measures</i>	<i>Anecdotal, no controls, off target end-points</i> OR <i>Not defensible in its class, insufficient data or measures</i>

A = Return of spontaneous circulation C = Survival to hospital discharge E = Other endpoint

B = Survival of event D = Intact neurological survival

Step 2C: Determine the direction of the results and the statistics: supportive? neutral? opposed?

DIRECTION of study by results & statistics:	SUPPORT the proposal	NEUTRAL	OPPOSE the proposal
Results	Outcome of proposed guideline superior, to a clinically important degree, to current approaches	Outcome of proposed guideline no different from current approach	Outcome of proposed guideline inferior to current approach

Step 2D: Cross-tabulate assessed studies by a) level, b) quality and c) direction (ie, supporting or neutral/ opposing); **combine and summarize.** Exclude the *Poor* and *Unsatisfactory* studies. Sort the *Excellent*, *Good*, and *Fair* quality studies by both *Level and Quality of evidence*, and *Direction of support* in the summary grids below. Use citation marker (e.g. author/ date/source). In the *Neutral* or *Opposing* grid use bold font for *Opposing* studies to distinguish them from merely neutral studies. Where applicable, please use a superscripted code (shown below) to categorize the primary

endpoint of each study.

Supporting Evidence

Serum glucose levels should be maintained within a normal range following intensive resuscitation in the term infant to minimize the potential risk for brain injury

Quality of Evidence	Excellent							
	Good			Salhab, 2004 D		Myers ,1977*E Vannucci,1980 E Yager,1992, D Sheldon 1992 E Chang 1999 D Park 2001 D Voorhies ,1986 D Laptook 1992 E Rosenberg 1990 E LeBlanc, 1994 D McGowan 1995 E Vannucci 1996 E Vannucci, 1996 D		

	Fair				Ondoa-Onama -2003 E	Lin 1996 D	Brambrink, E 1999		
		1	2	3	4	5	6	7	8
Level of Evidence									

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

Neutral or Opposing Evidence

Serum glucose levels should be maintained within a normal range following intensive resuscitation in the term infant to minimize the potential risk for brain injury

Quality of Evidence	Excellent								
	Good								
	Fair						Hattori, 1990 E		
			1	2	3	4	5	6	7 8
Level of Evidence									

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

STEP 3. DETERMINE THE CLASS OF RECOMMENDATION. Select from these summary definitions.

CLASS	CLINICAL DEFINITION	REQUIRED LEVEL OF EVIDENCE
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Class I <i>Definitely recommended.</i> Definitive, excellent evidence provides support.	<ul style="list-style-type: none"> • Always acceptable, safe • Definitely useful • Proven in both efficacy & effectiveness • Must be used in the intended manner for proper clinical indications. 	<ul style="list-style-type: none"> • One or more Level 1 studies are present (with rare exceptions) • Study results consistently positive and compelling
Class II: <i>Acceptable and useful</i>	<ul style="list-style-type: none"> • Safe, acceptable • Clinically useful • Not yet confirmed definitively 	<ul style="list-style-type: none"> • Most evidence is positive • Level 1 studies are absent, or inconsistent, or lack power • No evidence of harm
<ul style="list-style-type: none"> • Class IIa: <i>Acceptable and useful</i> Good evidence provides support	<ul style="list-style-type: none"> • Safe, acceptable • Clinically useful • Considered treatments of choice 	<ul style="list-style-type: none"> • Generally higher levels of evidence • Results are consistently positive
<ul style="list-style-type: none"> • Class IIb: <i>Acceptable and useful</i> Fair evidence provides support	<ul style="list-style-type: none"> • Safe, acceptable • Clinically useful • Considered optional or alternative treatments 	<ul style="list-style-type: none"> • Generally lower or intermediate levels of evidence • Generally, but not consistently, positive results
Class III: <i>Not acceptable, not useful, may be harmful</i>	<ul style="list-style-type: none"> • Unacceptable • Not useful clinically • May be harmful. 	<ul style="list-style-type: none"> • No positive high level data • Some studies suggest or confirm harm.
Indeterminate	<ul style="list-style-type: none"> • Research just getting started. • Continuing area of research • No recommendations until further research 	<ul style="list-style-type: none"> • Minimal evidence is available • Higher studies in progress • Results inconsistent, contradictory • Results not compelling

STEP 3: DETERMINE THE CLASS OF RECOMMENDATION. State a **Class of Recommendation** for the Guideline Proposal. State either **a) the intervention**, and then the conditions under which the intervention is either Class I, Class IIA, IIB, etc.; or **b) the condition**, and then whether the intervention is Class I, Class IIA, IIB, etc.

Indicate if this is a **Condition** or **Intervention**

Final Class of recommendation: **Class I-Definitely Recommended** **Class IIa-Acceptable & Useful; good evidence** **Class IIb-Acceptable & Useful; fair evidence** **Class III – Not Useful; may be harmful** **Indeterminate-minimal evidence or inconsistent**

REVIEWER’S PERSPECTIVE AND POTENTIAL CONFLICTS OF INTEREST: Briefly summarize your professional background, clinical specialty, research training, AHA experience, or other relevant personal background that define your perspective on the guideline proposal. List any potential conflicts of interest involving consulting, compensation, or equity positions related to drugs, devices, or entities impacted by the guideline proposal. Disclose any research funding from involved companies or interest groups. State any relevant philosophical, religious, or cultural beliefs or longstanding disagreements with an individual.

Neonatologist with 25 years of postgraduate experience. I underwent further research training in cerebral blood flow and metabolism. I have served on the Neonatal Resuscitation Program (NRP) for six years, and on the pediatric subcommittee of the AHA for four years. I have a potential conflict of interest in that I have written a manuscript on this subject (Salhab et al LOE 4) that was recently published and has now been included in the worksheet. However the original worksheet was done independent of the manuscript. The manuscript supports the original statement.

REVIEWER’S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK: Summarize your final evidence

integration and the rationale for the class of recommendation. Describe any mismatches between the evidence and your final Class of Recommendation. "Mismatches" refer to selection of a class of recommendation that is heavily influenced by other factors than just the evidence. For example, the evidence is strong, but implementation is difficult or expensive; evidence weak, but future definitive evidence is unlikely to be obtained. Comment on contribution of animal or mechanical model studies to your final recommendation. Are results within animal studies homogeneous? Are animal results consistent with results from human studies? What is the frequency of adverse events? What is the possibility of harm? Describe any value or utility judgments you may have made, separate from the evidence. For example, you believe evidence-supported interventions should be limited to in-hospital use because you think proper use is too difficult for pre-hospital providers. Please include relevant key figures or tables to support your assessment.

Clinical studies of acute ischemic stroke in adults support the conclusions of most adult experimental studies that preischemic **hyperglycemia** aggravates postischemic outcome (Payne, 2003, Kent, 2001, Margulies, 1994). It has become the cornerstone of the lactic acid hypothesis of cerebral ischemia since it provides a direct correlation between brain lactate levels and the degree of ischemic damage (Myers, 1977 #56)(LOE 6), Pulsinelli, 1982). Thus higher preischemic glucose levels lead to higher intras ischemic brain glucose levels and thus to greater postischemic brain damage. In studies of newborn animals, by contrast, 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 #47)(LOE 6). 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 #57)(LOE 6). 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).

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 et al, Le Blanc et al, Hattori et al (LOE 6)) One study indicates lower higher energy phosphate compounds as well as increased production of free radicals (Park et al) while three studies utilizing metabolic end points indicate preservation of CMRO₂ and ATP when glucose is maintained at high levels following ischemia (Laptook et al, Vannucci, Rosenberg (LOE 6)).

During or after hypoxia-ischemia, immature brain tissue appears to be specifically vulnerable to **hypoglycemia** as shown in neonatal animals (Vannucci et al, Brambrink(LOE 6)). Moreover the method of inducing hypoglycemia may influence outcome. Thus animals subjected to hypoglycemia induced by insulin versus fasting had greater mortality and a tendency towards enhanced neuropathologic morbidity (Yager et al(LOE 6)). However a second study utilizing this model failed to demonstrate this differential effect of insulin on outcome (Chang et al (LOE 6)). 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 et al, Ondoa-Onawa et al (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 > 40 mg/dL. Finally neuroimaging studies indicate a specific vulnerability of brain i.e. parietal-

occipital deep white and grey matter in association with hypoglycemia (Barkowitz et al, Mirukami et al).

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.

Preliminary draft/outline/bullet points of Guidelines revision: Include points you think are important for inclusion by the person assigned to write this section. Use extra pages if necessary.

Attachments:

Bibliography in electronic form using the Endnote Master Library. It is recommended that the bibliography be provided in annotated format. This will include the article abstract (if available) and any notes you would like to make providing specific comments on the quality, methodology and/or conclusions of the study.

Citation List

Citation Marker	Full Citation*
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{Brambrink, 1999 #51 }	Brambrink AM, Ichord RN, Martin LJ, Koehler RC, Traystman RJ. Poor outcome after hypoxia-ischemia in newborns is associated with physiological abnormalities during early recovery. Possible relevance to secondary brain injury after head trauma in infants. <i>Exp Toxicol Pathol.</i> 1999;51:151-62.
{Chang, 1999 #87 }	Chang YS, Park WS, Ko SY, Kang MJ, Han JM, Lee M, Choi J-H. Effects of fasting and insulin-induced hypoglycemia on brain cell membrane function and energy metabolism during hypoxia-ischemia in newborn piglets. <i>Brain Research.</i> 1999;844:135-142.
{Hattori, 1990 #48 }	Hattori H, Wasterlain CG. Posthypoxic glucose supplement reduces hypoxic-ischemic brain damage in the neonatal rat. <i>Ann Neurol.</i> 1990;28:122-8.
{Laptook, 1992 #55 }	Laptook AR, Corbett RJ, Arencibia-Mireles O, Ruley J. Glucose-associated alterations in ischemic brain metabolism of neonatal piglets. <i>Stroke.</i> 1992;23:1504-11.
{LeBlanc, 1994 #46 }	LeBlanc MH, Huang M, Patel D, Smith EE, Devidas M. Glucose given after hypoxic ischemia does not affect brain injury in piglets. <i>Stroke.</i> 1994;25:1443-7;
{Lin, 1996 #59 }	Lin Y, Greisen G. Analysis of the risk of brain damage in asphyxiated infants. <i>J Perinat Med.</i> 1996;24:581-9.
{McGowan, 1995 #92 }	McGowan JE, Marro PJ, Mishra OP, Delivoria-Papadopoulos M. Brain cell membrane function during hypoxia in hyperglycemic newborn piglets. <i>Pediatric Research.</i> 1995;37:133-139.
{Myers, 1977 #56}*	Myers RE, Yamaguchi S. Nervous system effects of cardiac arrest in monkeys. Preservation of vision. <i>Arch Neurol.</i> 1977;34:65-74.
{Mir, 1989 #58 }	Mir NA, Faquih AM, Legnain M. Perinatal risk factors in birth asphyxia: relationship of obstetric and neonatal complications to neonatal mortality in 16,365 consecutive live births. <i>Asia Oceania J Obstet Gynaecol.</i> 1989;15:351-7.
{Ondoa-Onama, 2003 #94 }	Ondoa-Onama C, Tumwine JK. Immediate outcome of babies with low Apgar score in Mulago Hospital, Uganda. <i>East Afr Med J.</i> 2003;80:22-9.
{Park, 2001 #50 }	Park WS, Chang YS, Lee M. Effects of hyperglycemia or hypoglycemia on brain cell membrane function and energy metabolism during the immediate reoxygenation-reperfusion period after acute transient global hypoxia-ischemia in the newborn piglet. <i>Brain Res.</i> 2001;901:102-8.
{Rosenberg, 1990 #53 }	Rosenberg AA, Murdaugh E. The effect of blood glucose concentration on postasphyxia cerebral hemodynamics in newborn lambs. <i>Pediatr Res.</i> 1990;27:454-9.
{Salhab, 2004 #256 }	Salhab, W. A., M. H. Wyckoff, et al. Initial hypoglycemia and neonatal brain injury in term infants with severe fetal acidemia. <u><i>Pediatrics</i></u> 2004; 114 (2): 361-6.
{Sheldon, 1992 #49 }	Sheldon RA, Partridge JC, Ferriero DM. Postischemic hyperglycemia is not protective to the neonatal rat brain. <i>Pediatr Res.</i> 1992;32:489-93.
	Vannucci RC, Brucklacher RM, Vannucci SJ. The effect of hyperglycemia on cerebral metabolism during hypoxia-ischemia in the immature rat. <i>J Cereb Blood Flow Metab.</i> 1996;16:1026-33.
	Vannucci RC, Nardis EE, Vannucci SJ. Cerebral metabolism during hypoglycemia and asphyxia in newborn dogs. <i>Biol Neonate.</i> 1980;38:276-86.
	Vannucci, R. C., A. Rossini, et al. Effect of hyperglycemia on ischemic brain damage during hypothermic circulatory arrest in newborn dogs. <u><i>Pediatr Res</i></u> 1996; 40 (2): 177-84.

<p>{ Vannucci, 1996 #57 }</p>	<p>Voorhies TM, Rawlinson D, Vannucci RC. Glucose and perinatal hypoxic-ischemic brain damage in the rat. <i>Neurology</i>. 1986;36:1115-8.</p>
<p>{ Vannucci, 1980 #54 }</p>	<p>Yager JY, Heitjan DF, Towfighi J, Vannucci RC. Effect of insulin-induced and fasting hypoglycemia on perinatal hypoxic-ischemic brain damage. <i>Pediatr Res</i>. 1992;31:138-42.</p>
<p>{ Vannucci, 1996 #257 }</p>	
<p>{ Voorhies, 1986 #47 }</p>	
<p>{ Yager, 1992 #52 }</p>	

*Type the citation marker in the first field and then paste the full citation into the second field. You can copy the full citation from EndNote by selecting the citation, then copying the FORMATTED citation using the short cut, Ctrl-K. After you copy the citation, go back to this document and position the cursor in the field, then paste the citation into the document (use Ctrl-V). For each new citation press Tab to move down to start a new field.

Hypoglycemia

Brambrink AM, Ichord RN, Martin LJ, Koehler RC, Traystman RJ. Poor outcome after hypoxia-ischemia in newborns is associated with physiological abnormalities during early recovery. Possible relevance to secondary brain injury after head trauma in infants. *Exp Toxicol Pathol.* 1999;51:151-62. (LOE 6)

Studies on hypoxic/asphyxic cardiac arrest in neonatal piglets (n=17), have defined predictors of short-term outcome using specific physiologic abnormalities immediately after the insult. One to two week old piglets were subjected to an asphyxial insult (room air O₂ + complete airway occlusion x 7 minutes) with loss of circulation by 5 to 6 minutes. Resuscitation included CPR, epinephrine -ROSC was defined as a MABP > 60 mmHg. Neurologic evaluations were performed at 6,12,24,36,48 and 96 hours. Neuropathology was performed on survivors at 4 days (n=10). Neurologic deficit at 24 hours (n=17) was correlated with the early metabolic status during the early reperfusion period. Low serum glucose levels, severe acidosis, and fever after resuscitation were associated with an adverse neurologic recovery one day after the insult. The occurrence of clinically apparent seizure activity during later recovery increased mortality (epileptic state), and survivors had greater neocortical and striatal brain damage.

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.

Level of Evidence 6

Quality fair

Evidence - supportive

Chang YS, Park WS, Ko SY, Kang MJ, Han JM, Lee M, Choi J-H. Effects of fasting and insulin-induced hypoglycemia on brain cell membrane function and energy metabolism during hypoxia-ischemia in newborn piglets. *Brain Research.* 1999;844:135-142.(LOE 6)

Objective: 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. **Results.** 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+, 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).

Conclusions 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

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

Level of Evidence 6-

Quality Good

Evidence - supportive

Lin Y, Greisen G. Analysis of the risk of brain damage in asphyxiated infants. J Perinat Med. 1996;24:581-9.

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 of 198 infants, ≥ 35 weeks of gestation, 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 at 12 months by report or those with mild handicap.

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

Mir NA, Faquih AM, Legnain M. Perinatal risk factors in birth asphyxia: relationship of obstetric and neonatal complications to neonatal mortality in 16,365 consecutive live births. Asia Oceania J Obstet Gynaecol. 1989;15:351-7.

Over a period of one year, 16,365 consecutively live born neonates were prospectively studied for evidence of birth asphyxia using the requirement of \geq one minute of positive pressure ventilation for identifying infants suffering from birth asphyxia. Asphyxia occurred in 2.8% of all neonates. Multivariate analysis of high risk factors associated with increased risk of asphyxia showed that low birth weight was the most significant predictor of asphyxia: asphyxia occurred in 68% of infants of less than 1,000 g birth weight and decreased to 1.2% in infants of 3-4 kg birth weight. Perinatal risk factors associated with a higher incidence of asphyxia include: postmaturity, birth weight (less than or equal to 2.5 kg) and with the presence of maternal and/or obstetric complications. The impact of asphyxia on neonatal mortality was most pronounced in more mature infants and the mortality was increased 3 fold in infants of less than 34 week gestation and greater than 27 fold for infants greater than 38 week gestation. Of the asphyxiated neonates, intrauterine growth retardation, fetal macrosomia, hypothermia, hyaline membrane disease, seizures, hypoglycemia and hyponatremia were significantly associated with an increased risk of death.

*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

Ondoa-Onama C, Tumwine JK. Immediate outcome of babies with low Apgar score in Mulago Hospital, Uganda. East Afr Med J. 2003;80:22-9.

BACKGROUND: Birth asphyxia contributes significantly to perinatal morbidity and mortality especially in resource poor

countries. Although. **OBJECTIVE:** To determine the prevalence of low Apgar score and establish immediate outcome and possible risk factors for poor 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%, hypoxaemia 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.

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

Salhab, W. A., M. H. Wyckoff, et al. Initial hypoglycemia and neonatal brain injury in term infants with severe fetal acidemia. *Pediatrics* 2004; 114(2): 361-6.

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 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.

Critique: Retrospective study in a high risk newborn population for brain injury. Hypoglycemia defined as

a blood sugar \leq 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

Vannucci RC, Nardis EE, Vannucci SJ. Cerebral metabolism during hypoglycemia and asphyxia in newborn dogs. *Biol Neonate*. 1980;38:276-86.

The cerebral metabolic responses to perinatal hypoglycemia (blood glucose \leq 20mg/dl) 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.

Critique: Metabolic end points with no neuropathologic data.

Level of Evidence 6

Quality fair

Evidence – supportive

Yager JY, Heitjan DF, Towfighi J, Vannucci RC. Effect of insulin-induced and fasting hypoglycemia on perinatal hypoxic-ischemic brain damage. *Pediatr Res*. 1992; 31:138-42.

The objectives were to determine whether hypoglycemia is protective or deleterious to the perinatal brain subjected to hypoxia-ischemia. 7-day postnatal rats were rendered hypoglycemic either by receiving a subcutaneous injection of insulin (n=27) or fasting for 12 h (n=24). Control animals (no insulin or fasting) (n=25) received subcutaneous injections of normal saline. All rat pups underwent unilateral common carotid artery ligation followed by exposure to 8% oxygen-balance nitrogen at 37 degrees C for 2 h. Mean blood glucose concentrations were 100, 80, and 60mg/dl 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 ($p < 0.001$). Mortality rates during hypoxia-ischemia were higher in the insulin-treated animals (30%) than in either the fasted (4%) or control (0%) animals ($p < 0.05$). 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.

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 6

Quality Good –fair

Evidence - supportive

Hyperglycemia

Hattori H, Wasterlain CG. Posthypoxic glucose supplement reduces hypoxic-ischemic brain damage in the neonatal rat. *Ann Neurol*. 1990;28:122-8.

The effect of posthypoxic glucose supplement in a neonatal hypoxic-ischemic animal model was evaluated. Seven-day-old rats underwent bilateral ligation of the carotid arteries, followed by exposure to an 8% oxygen atmosphere for 1 hour. Glucose was administered immediately following the insult (n=15), saline (n=15) and at one hour post insult glucose (n=10) saline (n=10). The extent of hypoxic-ischemic brain damage was assessed histologically 72 hours later. Glucose load (blood glucose level 350 to 400mg/dl) 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. This effect was not observed when glucose was administered one hour later. 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.

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 6

Quality Fair

Evidence Neutral

Laptook AR, Corbett RJ, Arencibia-Mireles O, Ruley J. Glucose-associated alterations in ischemic brain metabolism of neonatal piglets. *Stroke*. 1992;23:1504-11.

The study objectives were to determine in neonatal piglets 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 (CBF) 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 CBF were comparably distributed between groups and ranged from 15% to 110% of those of control. **At a given reduction of CBF hyperglycemic piglets maintained a higher concentration of beta-ATP** (p = 0.011) and had a smaller increase in inorganic phosphorus (p < 0.001). At CBF < 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. CONCLUSION: It was concluded that ATP preservation may in part account for the differing effects of glucose during ischemia in neonates as compared with adults. However since there were no neuropathologic data it remains unclear whether the accentuated brain acidosis is not deleterious to neonatal brain tissue.

Critique: Protective effect of increased glucose in terms of ATP preservation but no neuropathologic data.

Level of Evidence 6

Quality Fair

Evidence - supportive

LeBlanc MH, Huang M, Patel D, Smith EE, Devidas M. Glucose given after hypoxic ischemia does not

affect brain injury in piglets.

Stroke. 1994;25:1443-7;

Hypothesis Providing glucose before hypoxic ischemia worsens brain injury in piglets. A second question addressed the issue of whether providing glucose after hypoxic ischemia affects 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 (n=21) followed by 2 mL/kg per hour for 2 hours or an equal volume of saline (n=22). **RESULTS:** The glucose level in the treatment group was 250mg/dl and in the normal saline group 100mg/dl. Neurological examination scores by blinded observer with normal score = 20 and brain dead score = 5. At 1 day post injury scores were similar in the two groups: i.e. for the glucose group the median score = 15.5 (25th percentile, 12.2; 75th percentile, 18) and for the controls the median score = 15.6 (9.3, 18). Piglets were euthanized at 3 days with brain preservation upon death. Pathological examination scores that were blinded and that incorporated the sum of scores from cortex, hippocampus, and basal ganglia. A normal score = 30 and total necrosis = 3. The scores were comparable in the two groups. Thus for the glucose group the score was 26 (18, 28) and for the controls 25 (16.5, 28). **CONCLUSIONS:** Although elevated glucose levels during hypoxic ischemic injury worsen brain injury in the piglet model, elevated glucose levels after injury do not affect the severity of the injury

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 6

Quality Good

Evidence - Neutral

McGowan JE, Marro PJ, Mishra OP, Delivoria-Papadopoulos M. Brain cell membrane function during hypoxia in hyperglycemic newborn piglets. *Pediatric Research*. 1995;37:133-139.

Hypothesis 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 blood 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. **Conclusions:** These data suggest that in the newborn piglet model hyperglycemia reduces hypoxia-induced brain cell dysfunction.

Level of Evidence 6-

Quality Good

Evidence - supportive

Myers RE, Yamaguchi S. Nervous system effects of cardiac arrest in monkeys. Preservation of vision. Arch

Neurol. 1977;34:65-74.

Thirteen juvenile monkeys were taught two visual discrimination tasks. After 12 to 24 hours of food deprivation, ten underwent 14-minute episodes of cardiac arrest. Three served as controls. Five of the ten arrested animals survived and were tested in the discrimination box. All continued to perform color and pattern discrimination tasks with one to eight days' delay. All appeared neurologically intact, while brain pathologic examination after 11 to 64 days' survival showed either intact brains or injury restricted to nuclear structures in the brain stem, cerebellar Purkinje cells, and hippocampus. Five animals died 4 to 36 hours after they were resuscitated. Two required prolonged cardiac massage and, despite return of adequate cardiovascular function, died early. A third animal dislodged its arterial catheter and exsanguinated. The remaining two animals, who received infusions of glucose just prior to arrest, developed widespread fasciculations and myoclonic seizures. They became decerebrate and opisthotonic and were killed after 10 and 36 hours. Their brains showed mild edema and widespread necrosis of cortex and basal ganglia. Thus, food-deprived monkeys tolerate 14 minutes of circulatory arrest well and show minimal neurologic and pathologic changes, while administration of glucose just before arrest markedly augments the severity of brain injury and alters its distribution

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 6

Quality Good to Fair

Evidence - Opposing

Park WS, Chang YS, Lee M. Effects of hyperglycemia or hypoglycemia on brain cell membrane function and energy metabolism during the immediate reoxygenation-reperfusion period after acute transient global hypoxia-ischemia in the newborn piglet. Brain Res. 2001;901:102-8.

Forty-five newborn piglets were divided randomly into four experimental groups: normoxia control (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 hours 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.

Results: During HI, heart rate, base deficit, glucose and lactate level in the blood and cerebrospinal 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 Hypoglycemia group. Cerebral Na(+),K(+)-ATPase activity decreased, and lipid peroxidation products increased significantly in HC group than in normoxia 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.

Conclusion. Hyperglycemia, but not hypoglycemia immediately after HI interfered with the recovery of brain cell membrane function and energy metabolism.

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 6

Quality Fair

Evidennce- Supportive

Rosenberg AA, Murdaugh E. The effect of blood glucose concentration on postasphyxia cerebral hemodynamics in newborn lambs. Pediatr Res. 1990;27:454-9.

The effect of pre-asphyxial blood glucose concentration on post-asphyxial (PA) cerebral hemodynamics was examined in 21 newborn lambs. Glucose was unregulated in one group - i.e. no effort was made to

control glucose in this group (n = 7), and controlled throughout the study by glucose clamp in hyperglycemic (n = 7) and hypoglycemic (n = 7) groups. Cerebral blood flow (CBF), 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. Pre-asphyxial blood glucose levels were 120, 210 and 45mg/dl in the three groups. In all three groups, 5 min Post asphyxial CBF was significantly increased from control. In the late period after asphyxia, the unregulated group had decreased CBF compared with control, 53.2 +/- 3.8 mL.100 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 post asphyxia, 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 less than 0.05; 200 +/- 4; and 181 +/- 10, p less than 0.05 at 1, 2, and 4 h, respectively, PA versus 251 +/- 12 at control. In the hypoglycemic group CMRO₂ was 170 +/- 9 microM.100 g-1.min-1, mean +/- SEM, p < 0.05; 174 +/- 14; p < 0.05 and 183 +/- 17, p < 0.05 at 1, 2, and 4 h, respectively, post asphyxia versus 231 +/- 12 at control. CMRO₂ did not differ from control in the hyperglycemic group at 1, 2 and 4 hour post asphyxia. Thus CMRO₂ was best maintained post asphyxia in the presence of hyperglycemia.

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

Level of Evidence 6

Quality Good

Evidence - supportive

Sheldon RA, Partridge JC, Ferriero DM. Postischemic hyperglycemia is not protective to the neonatal rat brain. *Pediatr Res.* 1992;32:489-93.

The role of glucose administration after ischemic neuronal damage to neonatal rat brain was evaluated in Sprague-Dawley rat pups at postnatal day 7. They were subjected to left common carotid artery ligation followed by 2.5 h of 8% oxygen using the Levine procedure. The experimental group was subdivided so that pups received either systemic injections of glucose (n=6) or saline (n=6) immediately after the hypoxic insult. A non surgical control group (n=4) for each glucose or saline was studied as well. Animals were killed on postnatal d 12 and brain areas of ipsilateral and contralateral cortex and caudate were calculated from camera lucida tracings. **Results:** Glucose levels in the glucose treated group ranged from 200 to 240mg/dl and in the saline group from 20 to 40 mg/dl. There was no significant difference in size of brain infarction between postischemic glucose-treated and post-ischemic saline-treated pups. However, hypoxic-ischemic brains did show more severe neuronal damage when hyperglycemia was induced after asphyxia.

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 6-

Quality - Good to Fair

Evidence - Supportive

Vannucci RC, Brucklacher RM, Vannucci SJ. The effect of hyperglycemia on cerebral metabolism during hypoxia-ischemia in the immature rat. *J Cereb Blood Flow Metab.* 1996;16:1026-33.

Hyperglycemia with circulating glucose concentrations of 25-35 mM/L (450 to 600 mg/dl) protects the immature brain from hypoxic-ischemic damage. The objectives were to determine the effect of hyperglycemia on cerebral oxidative metabolism during the course of hypoxia-ischemia. 7-day postnatal rats (n=5-6) underwent unilateral common carotid artery ligation followed by exposure to 8% O₂ for 2 h at 37 degrees C. Experimental animals (n=5-6) 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 (360-450mg/dl) 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 (CMR_{glc}) increased from 7.1 (control) to 20.2 $\mu\text{mol } 100 \text{ g}^{-1} \text{ min}^{-1}$ 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. The data 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 lactic acidosis, 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

Critique: Rat pup model. Non randomized. Power analysis for sample size not provided.

Level of Evidence 6

Quality – Good

Evidence - supportive

Vannucci, R. C., A. Rossini, et al. Effect of hyperglycemia on ischemic brain damage during hypothermic circulatory arrest in newborn dogs. *Pediatr Res* 1996; **40**(2): 177-84.

Aim The effect of hyperglycemia on ischemic brain damage was investigated in a newborn dog model of hypothermic circulatory arrest. **Methods** Newborn dogs were anesthetized with halothane, paralyzed, and artificially ventilated to maintain normoxia and acid-base balance. Animals were surface-cooled to 20 degrees C, after which cardiac arrest was effected with i.v. KCl. Before surface cooling, one-half of the dogs ($n = 12$) received a bolus injection of 50% glucose to increase plasma glucose concentrations to approximately 33 mmol/L (600 mg/dL); control littermates ($n = 12$) received an equivalent volume of 1 N saline. The dogs remained asystolic for 1.75 h, after which cardiopulmonary resuscitation was accomplished. **Results** All animals survived, were allowed to recover from anesthesia at 37 degrees C, and were maintained for 8 h of recovery, at which interval they underwent perfusion-fixation of their brains for pathologic analysis. Histologic grading of brain damage showed no statistically significant difference in the severity of neuronal necrosis within the cerebral cortex or caudate nucleus between hyperglycemic and normoglycemic littermates, with greater brain damage apparent in the amygdaloid nucleus of the hyperglycemic dogs ($p < 0.02$). Brainstem injury occurred more frequently in the hyperglycemic animals ($p < 0.05$). Correlation of coefficients analyses revealed a positive correlation between the severity of brain damage and plasma glucose concentration for both the caudate nucleus and amygdaloid nucleus but not for the cerebral cortex. **Conclusions** The findings suggest that hyperglycemia superimposed upon hypothermic circulatory arrest in the newborn dog accentuates brain damage only in selected regions of the brain, especially the caudate and amygdaloid nuclei and brainstem, excluding the cerebral cortex.

Critique – Large model – differential adverse of hyperglycemia within brain.

Level of Evidence 6

Quality – Good

Evidence - supportive

Voorhies TM, Rawlinson D, Vannucci RC. Glucose and perinatal hypoxic ischemic brain damage in the rat. *Neurology*. 1986;36:1115-8.

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 ($n=20$) (glucose levels 200 to 300mg/dl) survived more than twice as long as saline-treated littermates ($n=20$). 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.

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

Level of Evidence 6

Quality Fair

Evidence - Supportive

Selected Background Information

Payne RS, Tseng MT, Schurr A. The glucose paradox of cerebral ischemia: evidence for corticosterone involvement. *Brain Research*. 2003;971:9-17.

Aggravation of neuronal damage by preischemic hyperglycemia, i.e. the glucose paradox of cerebral ischemia, is a well-established phenomenon that has prompted clinicians around the world to closely monitor and control blood glucose levels in surgical cases at high risk for ischemic episodes. The widely prevalent idea that lactic acidosis is responsible for hyperglycemia-enhanced ischemic neuronal damage is challenged with the hypothesis that glucose-elicited corticosterone release is a more compelling explanation of the glucose paradox. Corticosterone is the main rodent glucocorticoid, and has important effects on glucose metabolism. Rats were exposed to 7 min of cardiac arrest-induced transient global ischemia. Plasma glucose and corticosterone (CT) levels were manipulated and monitored to assess their effects on delayed neuronal damage as measured 7 days postischemia using electrophysiological and histological methods. Seizure activity was assessed 24 h postischemia. The results demonstrate that the extent of postischemic neuronal damage correlates with plasma CT level, not glucose, at the onset of ischemia. Moreover, an elevation in plasma glucose levels triggers a significant increase in CT plasma levels. Pretreatment of hyperglycemic rats with the CT synthesis inhibitor metyrapone or the CT receptor antagonist, RU38486, prevents hyperglycemic aggravation of ischemic neuronal damage. The increased incidence of seizure and delayed neuronal damage resulting from preischemic hyperglycemia corresponds with CT levels rather than with glucose levels and suggests that CT has a greater prognostic value than glucose in predicting cerebral ischemic damage

Kent TA, Soukup VM, Fabian RH. Heterogeneity affecting outcome from acute stroke therapy: making reperfusion worse. *Stroke*. 2001;32:2318-27.

BACKGROUND: Stroke patients are heterogeneous not only with respect to etiology but also in terms of preexisting clinical conditions. Approximately one fifth of patients with acute stroke are hyperglycemic and/or have had a recent infectious or inflammatory condition. **Summary of Review--** Experimental research indicates that these factors can alter and accelerate the evolution of stroke and reperfusion injury, although these effects are complex and some may have a favorable impact. Both conditions involve activation of inflammatory and reactive oxygen mechanisms. In addition, **hyperglycemia** has concomitant deleterious vascular and metabolic effects that worsen infarct size and encourage hemorrhagic transformation in reperfusion models. Clinical data are less extensive but in general support an adverse impact on outcome. **CONCLUSIONS:** After examining these data in detail, we concluded that the presence of these clinical conditions could assist in identification of those at increased risk for complications of reperfusion therapy. Furthermore, consideration of these factors may provide a rational basis for combination therapy and improve the clinical relevance of experimental stroke models.

Margulies DR, Hiatt JR, Vinson D, Jr., Shabot MM. Relationship of hyperglycemia and severity of illness to neurologic outcome in head injury patients. *Am Surg*. 1994;60:387-90.

Hyperglycemia upon hospital admission has been associated with poorer neurologic outcomes in patients

with brain injury, but this relationship has not been well defined. To evaluate the relationship of hyperglycemia and severity of illness to neurologic outcome, the authors examined Surgical Intensive Care Unit (SICU) records for a 6 month period at a Level I trauma center. Of 276 trauma admissions, 97 patients had intracranial injuries. The peak glucose determination on the first day of admission was correlated with the Glasgow Coma Scale (GCS) score upon admission and discharge from the SICU and with severity of illness as measured by the Simplified Acute Physiology Score (SAPS). The mean admission GCS was 10.6 (+/- 0.49 S.E.M.), the mean glucose on the first SICU day was 146 (+/- 7.7 S.E.M.), and the mean peak glucose was 176 (+/- 8.2 S.E.M.). The peak glucose was inversely related to both GCS on admission and GCS at discharge ($P < 0.001$). However, stepwise multiple regression analysis revealed that the best single predictor of GCS at discharge was the GCS on admission. The next best predictor was the SAPS on the first SICU day. Peak glucose did not add to the power of admission GCS and SAPS to predict neurologic outcome. Peak glucose levels in brain-injured patients may simply reflect severity of illness and injury that is better represented by SAPS

Barkovich AJ, Ali FA, Rowley HA, Bass N. Imaging patterns of neonatal hypoglycemia. *AJNR Am J Neuroradiol.* 1998;19:523-8.

Objective: Our purpose was to report the patterns of injury observed in five patients who suffered brain damage consequent to neonatal hypoglycemia. **METHODS:** The imaging studies and clinical records of five patients with brain damage caused by neonatal hypoglycemia were reviewed retrospectively. Patterns of injury were compared with those described in the literature and those seen in neonatal hypoxic-ischemic injury. **RESULTS:** Diffuse cortical and subcortical white matter damage was seen, with the parietal and occipital lobes affected most severely. Globus pallidus injury was present in one patient who had the most severe cortical injury. **CONCLUSION:** We found a specific pattern of injury that correlates well with the sparse pathologic and imaging reports on neonatal hypoglycemia. We speculate that the patterns of damage are the result of regional hypoperfusion and excitatory toxicity with cell-type-specific injury

Murakami Y, Yamashita Y, Matsuishi T, Utsunomiya H, Okudera T, Hashimoto T. Cranial MRI of neurologically impaired children suffering from neonatal hypoglycaemia. *Pediatr Radiol.* 1999;29:23-7.

BACKGROUND: Metabolic disturbances such as anoxia and hypoglycaemia are important in causing maldevelopment of the neonatal brain. While there have been some pathology studies of the effects of neonatal hypoglycaemia on brain development, reports of MRI findings in such infants have been rare. **OBJECTIVES:** To describe the MRI findings in neurologically handicapped children who had suffered from neonatal hypoglycaemia and to evaluate the relationship between the neurological impairment and neonatal hypoglycaemia. **METHODS:** We retrospectively evaluated the MRI findings in eight full-term infants with neonatal symptomatic hypoglycaemia who later exhibited neurological handicap. The age at which the MRI scans were obtained ranged from 9 months to 8 years 10 months (mean 4 years 1 month, median 4 years). **RESULTS:** The most striking findings were prolonged T1 weighting and T2 weighting in the parieto-occipital periventricular deep white matter in six patients, suggesting abnormal or delayed myelination. Dilatation of the lateral ventricles, especially of the trigones, was observed in five patients in whom the distance between the posterior horns of the lateral ventricles and the adjacent sulci was reduced. The volume of white matter relative to grey matter was reduced in two patients. In addition, four patients exhibited cerebral cortical atrophy, mainly in the occipital lobe. **CONCLUSIONS:** These findings suggest that neonatal hypoglycaemia may cause delayed or abnormal myelination, especially in the parieto-occipital, periventricular, deep white matter, and may cause cerebral cortical atrophy, especially in the occipital lobe.

Booth RF, Patel TB, Clark JB. The development of enzymes of energy metabolism in the brain of a precocial (guinea pig) and non-precocial (rat) species. *J Neurochem.* 1980;34:17-25. Key enzymes of ketone body metabolism (3-hydroxybutyrate dehydrogenase, 3-oxo-acid:CoA transferase, acetoacetyl-CoA thiolase) and glucose metabolism (hexokinase, lactate dehydrogenase, pyruvate dehydrogenase, citrate synthase) have been measured in the brains of foetal, neonatal, and adult guinea pigs and compared to those in the brains of neonatal and adult rats. The activities of the guinea pig brain ketone-body-metabolising enzymes remain relatively low in activity throughout the foetal and neonatal periods, with only slight increases occurring at birth. This contrasts with the rat brain, where three- to fourfold

increases in activity occur during the suckling period (0-21 days post partum), followed by a corresponding decrease in the adult. The activities of the hexokinase (mitochondrial and cytosolic), pyruvate dehydrogenase, lactate dehydrogenase, and citrate synthase of guinea pig brain show marked increases in the last 10-15 days before birth, so that at birth the guinea pig possesses activities of these enzymes similar to the adult state. This contrasts with the rat brain where these enzymes develop during the late suckling period (10-15 days after birth). The development of the enzymes of aerobic glycolytic metabolism correlate with the onset of neurological competence in the two species, the guinea pig being a "precocial" species born neurologically competent and the rat being a "non-precocial" species born neurologically immature. The results are discussed with respect to the enzymatic activities required for the energy metabolism of a fully developed, neurologically competent mammalian brain and its relative sensitivity to hypoxia.

Pulsinelli WA, Waldman S, Rawlinson D, Plum F. Moderate hyperglycemia augments ischemic brain damage: a neuropathologic study in the rat. *Neurology*. 1982;32:1239-1246.

Methods: The effects of glucose injection with those of saline or mannitol on ischemic brain damage and brain water content in a four-vessel occlusion (4-VO) rat model, which simultaneously causes severe forebrain ischemia and moderate hindbrain ischemia was compared. **Results:** Glucose given prior to the onset of ischemia was followed by severe brain injury, with necrosis of the majority of neocortical neurons and glia, substantial neuronal damage throughout the remainder of forebrain, and severe brain edema. By

comparison, saline injection before forebrain ischemia resulted in only scattered ischemic damage confined to neurons and no change in the brain water content. Mannitol injection before 4-VO or D-glucose injection during or after 4-VO produced no greater forebrain damage than did the saline injection. Morphologic damage in the cerebellum, however, was increased by D-glucose injection given either before or during 4-VO. **Conclusions** Hyperglycemia before severe brain ischemia or during moderate ischemia markedly augments morphologic brain damage.