

**WORKSHEET for PROPOSED Evidence-Based GUIDELINE RECOMMENDATIONS**

<b>Worksheet Author:</b>	<b>Taskforce/Subcommittee:</b> __BLS __ACLS x PEDS __ID __PROAD __x_Other: NRP
<b>Author's Home Resuscitation Council:</b> __x_AHA __ANZCOR __CLAR __ERC __HSFC __HSFC __RCSA __IAHF __Other:	<b>Date Submitted to Subcommittee:</b> 8/11/04

**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**

Although several recent animal and human studies have suggested that selective cerebral hypothermia may protect against brain injury in the asphyxiated infant, we cannot recommend routine implementation of this therapy until appropriate controlled randomized studies have been performed. (Class of Recommendation-Indeterminate)

**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).**

Selective and/or whole body modest hypothermia implemented in the first six hours of postnatal life in term infants at highest risk for evolving to moderate to severe encephalopathy will reduce the subsequent development of irreversible brain injury without untoward side effects

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

**Mesh terms** included hypothermia, induced hypothermia, body cooling, whole body cooling, selective body cooling, neonate, neonate , asphyxia, hypoxia ischemia, body temperature, animal, seizures brain diseases

**Medline: (1966-2004)** Hypothermia + Hypoxia-ischemia – 57 hits of which 30 were reviewed, Hypoxia-Ischemia + Newborn +hypothermia- 16 hits-15 were reviewed, Asphyxia + hypothermia-6 hits- all reviewed, Induced hypothermia+ newborn- 8 hits-all reviewed, whole body cooling –74 hits-4 reviewed, seizures +hypothermia+ newborn- 8 hits-4 reviewed

**Embase:** Asphyxia+ hypothermia- 134 hits-27 reviewed, asphyxia+ body temperature- 27 hits-6 reviewed, asphyxia+newborn+hypothermia-58hits-22 were reviewed, induced hypothermia+ newborn- 114 hits-36 were reviewed, induced hypothermia + hypoxia-ischemia – 15 hits-11 were reviewed, hypothermia + hypoxia-ischemia- 57 hits- 29 were reviewed, newborn + neuroprotection + hypoxia-ischemia – 71 hits- 3 were reviewed, induced hypothermia+ neuroprotection +newborn- 18 hits – 14 were reviewed

There is one relevant **Cochrane review**

Cooling for Newborns with hypoxic –ischemic encephalopathy- Jacobs, s et al Cooling for newborns with hypoxic ischaemic encephalopathy (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2004.

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. Pubmed, Embase, Cochrane database ECC library, Review articles

Medline Pubmed, ECC endnote library, Cochrane Systematic database Reviews, Embase, References, Review articles

- 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 adult animal studies, no abstracts

- 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.

66 articles met criteria for further review and 25 were included in this worksheet

**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.

<b>Level of Evidence</b>	<b>Definitions</b> (See manuscript for full details)
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<b>Level 1</b>	
<b>Level 2</b>	Akisu, 2003, Gunn, 1998, Shankaran, 2002, Zhou, 2002
<b>Level 3</b>	Battin, 2001, Battin, 2003
<b>Level 4</b>	Compagnoni, 2002
<b>Level 5</b>	Azzopardi, 2000 , Debillon, 2003, Kilani, 2002
<b>Level 6</b>	Bona, 1998 Gunn, 1997, Gunn,, 1998 ,Gunn, 1999, Haaland, 1997, Laptook, 1997 Laptook, 1999, Taylor, 2002, Thoresen, 2001 Thoresen, 2001, Tooley, 2003, Wagner, 2002
<b>Level 7</b>	Bernard, 2002, Horan, 2004, , The Hypothermia after Cardiac Arrest Study Group, 2002
<b>Level 8</b>	

**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.

<b>Component of Study and Rating</b>	<b>Excellent</b>	<b>Good</b>	<b>Fair</b>	<b>Poor</b>	<b>Unsatisfactory</b>
<b>Design &amp; Methods</b>	Highly appropriate sample or model, randomized, proper controls <b>AND</b> Outstanding accuracy, precision, and data collection in its class	Highly appropriate sample or model, randomized, proper controls <b>OR</b> Outstanding accuracy, precision, and data collection in its class	Adequate, design, but possibly biased <b>OR</b> Adequate under the circumstances	<i>Small or clearly biased population or model</i> <b>OR</b> <i>Weakly defensible in its class, limited data or measures</i>	<i>Anecdotal, no controls, off target end-points</i> <b>OR</b> <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?**

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

	current approaches		approach
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**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

**Selective and/or whole body modest hypothermia implemented in the first six hours of postnatal life in term infants at highest risk for evolving to moderate to severe encephalopathy will reduce the subsequent development of irreversible brain injury without untoward side effects**

<b>Quality of Evidence</b>	<b>Excellent</b>						Gunn, 1997	The Hypothermia after Cardiac Arrest Study Group, 2002 <b>D</b>
	<b>Good</b>						Bona, 1998 Gunn, 1998  Haaland, 1997 Laptook, 1997 Taylor, 2002  Thoresen, 2001  Tooley, 2003  Wagner, 2002	{Bernard, 2002 <b>D</b>
	<b>Fair</b>	Akisu, 2003 <b>E</b> Gunn, 1998 <b>E</b> Shankaran, 2002 <b>E</b> Zhou, 2002 <b>E</b>	Battin, 2001 <b>E</b> Battin, 2003 <b>E</b>	Compagnoni 2002 <b>E</b>		Azzopardi, 2000 <b>E</b> Debillon, 2003 <b>E</b> Kilani, 2000 <b>E</b>		Horan, 2004 <b>E</b>
	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>	<b>8</b>
<b>Level of Evidence</b>								

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

**Selective and/or whole body modest hypothermia implemented in the first six hours of postnatal life in term infants at highest risk for evolving to moderate to severe encephalopathy will reduce the subsequent development of irreversible brain injury without untoward side effects**

<b>Quality of Evidence</b>	<b>Excellent</b>								
	<b>Good</b>						Gunn, 1998 <b>E</b> Gunn, 1999 <b>E</b> Laptook, 1999 <b>E</b> Thoresen, 2001 <b>E</b>		
	<b>Fair</b>								
		<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>	<b>8</b>
		<b>Level of Evidence</b>							

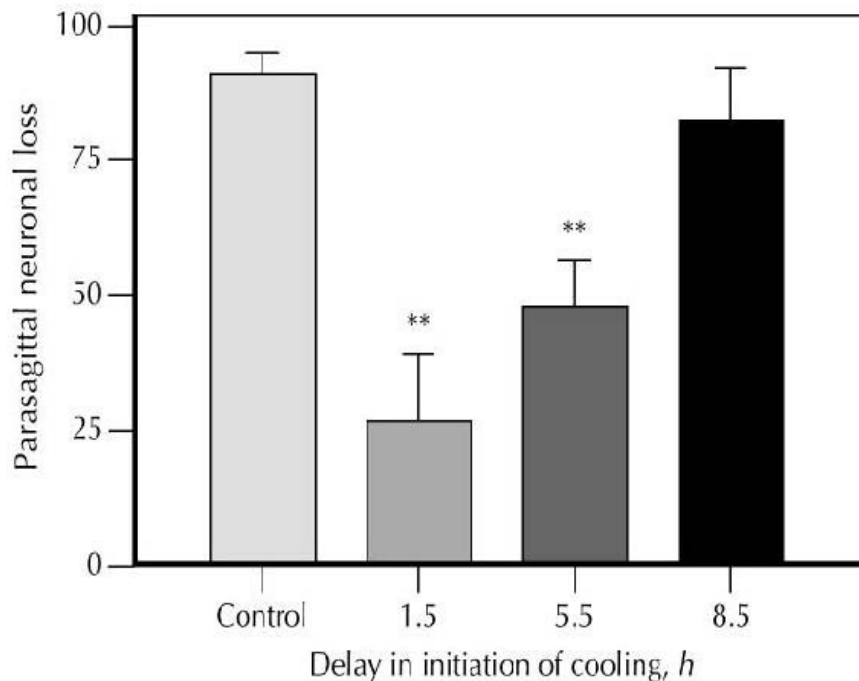
A = Return of spontaneous circulation C = Survival to hospital discharge E = Other endpoint  
B = Survival of event D = Intact neurological survival

**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. Research training in cerebral blood flow and metabolism. Have served on the Neonatal Resuscitation Program (NRP) for six years, and on the pediatric subcommittee of the AHA. I have a no potential conflict of interest.

**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.

Modest systemic or selective cooling of the brain by as little as 2°-4° C has been shown to reduce the extent of tissue injury in experimental studies as well as in humans following brain injury events such as stroke, trauma or cardiac arrest {Bona, 1998 #167} (Gunn, 1997 #161){Gunn, 1998 #162}{Laptook, 1997 #165}{Laptook, 1999 #166}{Thoresen, 2001 #243}{Thoresen, 2001 #244}{Tooley, 2003 #242}{Wagner, 2002 #230}LOE 6), {Bernard, 2002 #240}{The Hypothermia after Cardiac Arrest Study Group, 2002 #237}LOE 7 for neonates). Potential mechanisms of neuroprotection with hypothermia include inhibition of glutamate release, reduction of cerebral metabolism which in turn preserves high energy phosphates, decrease in intracellular acidosis and lactic acid accumulation, preservation of endogenous antioxidants, reduction of nitric oxide production, prevention of protein kinase inhibition, improvement of protein synthesis, reduction of leukotriene production (Akisu, 2003 LOE 6), prevention of blood brain barrier disruption and brain edema and inhibition of apoptosis(Zhu, 2004 (LOE 6) . Although neuroprotection following intra-ischemic hypothermia is well established, the effects of post-ischemic hypothermia has been less certain. The latter is the typical scenario in the human newborn. Clearly, the sooner hypothermia can be initiated, the more likely it is to be successful ( Gunn 1998-see below, Laptook, 1997)



. Selective head cooling is attractive because it reduces potential side effects but is associated with differential gradients within the brain .Total body cooling is more likely to be associated with side effects but less temperature gradient within the brain. A major concern of hypothermia in newborn infants relates to potential adverse effects including hypoglycemia, reduction of myocardial contractility and ventilation-perfusion mismatch, increased blood viscosity, acid-base and electrolyte imbalance and an increased risk of

infection. Several pilot studies in neonates at risk for hypoxic ischemic brain injury that have utilized both selective head as well as whole body cooling have shown that modest hypothermia to be without major side effects (Azzopardi, 2000 #203), (Battin, 2003 #233), (Compagnoni, 2002 #227), (Gunn, 1998 #163), (Shankaran, 2002 #231), (Simbruner, 1999 #228), (Zhou, 2002 #224) (LOE 3,4,7.). Subsequently two large randomized multicenter studies have been undertaken and completed in term infants at highest risk for evolving to moderate and/or severe encephalopathy, using either selective or systemic modest hypothermia. One of these studies utilizing selective head cooling has reported follow up results at 18 months (oral communication). No effect of hypothermia with regard to the development of cerebral palsy and/or death was observed for all infants treated. However for infants who presented with moderate encephalopathy and without seizures, a significant benefit of hypothermia was noted. No effect was observed in those infants with severe encephalopathy and/or early seizures. Several critical questions need to be addressed as a consequence of these preliminary data: 1) What is the ideal temperature for selective head cooling? 2) Which is the best mode of inducing hypothermia, i.e., selective head versus total body cooling? 3) How long should hypothermia be maintained? 4) Will a multimodal approach especially for the more severely affected infants be more effective than hypothermia alone?

**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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{ Akisu, 2003 #222 }	Akisu, M., A. Huseyinov, et al. Selective head cooling with hypothermia suppresses the generation of platelet-activating factor in cerebrospinal fluid of newborn infants with perinatal asphyxia. <u>Prostaglandins Leukotrienes &amp; Essential Fatty Acids</u> . 2003 69(1): 45-50.
{ Azzopardi, 2000 #203 }	Azzopardi, D., N. J. Robertson, et al. Pilot study of treatment with whole body hypothermia for neonatal encephalopathy. <u>Pediatrics</u> 2000; <b>106</b> (4): 684-94.
{ Battin, 2001 #232 }	Battin, M. R., J. A. Dezoete, et al. Neurodevelopmental outcome of infants treated with head cooling and mild hypothermia after perinatal asphyxia. <u>Pediatrics</u> 2001 107(3): 480-4.
{ Battin, 2003 #233 }	
{ Bernard, 2002 #240 }	Battin, M. R., J. Penrice, et al. Treatment of term infants with head cooling and mild systemic hypothermia (35.0 degrees C and 34.5 degrees C) after perinatal asphyxia. <u>Pediatrics</u> 2003;111(2): 244-51.
{ Bona, 1998 #167 }	Bernard, S. A., T. W. Gray, et al. Treatment of Comatose Survivors of Out-of-Hospital Cardiac Arrest with Induced Hypothermia. <u>N Engl J Med</u> 2002; 346(8): 557-563.
{ Compagnoni, 2002 #227 }	Bona, E., H. Hagberg, et al. Protective effects of moderate hypothermia after neonatal hypoxia-ischemia: short- and long-term outcome. <u>Pediatr Res</u> 1998 ;43(6): 738-45.
{ Debillon, 2003 #137 }	Compagnoni, G., L. Pogliani, et al. Hypothermia reduces neurological damage in asphyxiated newborn infants. <u>Biol Neonate</u> 2002; 82(4): 222-7.
{ Gunn, 1997 #161 }	Debillon, T., P. Daoud, et al. Whole-body cooling after perinatal asphyxia: A pilot study in term neonates. <u>Developmental Medicine &amp; Child Neurology</u> 2003; 45(1): 17-23.
{ Gunn, 1998 #162 }	
{ Gunn, 1999 #169 }	Gunn, A. J., T. R. Gunn, et al. Dramatic neuronal rescue with prolonged selective head cooling after ischemia in fetal lambs. <u>Journal of Clinical Investigation</u> 1997; 99(2): 248-256.
{ Gunn, 1998 #163 }	Gunn, A. J., T. R. Gunn, et al. Neuroprotection with prolonged head cooling started before postischemic seizures in fetal sheep. <u>Pediatrics</u> 1998; 102(5): 1098-1106.
{ Haaland, 1997 #246 }	Gunn, A. J., L. Bennet, et al. Cerebral hypothermia is not neuroprotective when started after postischemic seizures in fetal sheep. <u>Pediatr Res</u> 1999;46(3): 274-80.
{ Horan, 2004 #221 }	Gunn, A. J., P. D. Gluckman, et al. Selective head cooling in newborn infants after perinatal asphyxia: A safety study. <u>Pediatrics</u> 1998; 102(4 I): 885-892.
{ Kilani, 2002 #250 }	Haaland, K., E. M. Loberg, et al. Posthypoxic hypothermia in newborn piglets. <u>Pediatr Res</u> 1997 41(4 Pt 1): 505-12.
{ Laptook, 1997 #165 }	Horan, M., S. Ichiba, et al. A pilot investigation of mild hypothermia in neonates receiving extracorporeal membrane oxygenation (ECMO). <u>Journal of Pediatrics</u> 2004;144(3): 301-308.
{ Laptook, 1999 #166 }	
{ Shankaran, 2002 #231 }	Kilani, R. A. (2002). "The safety and practicality of selective head cooling in asphyxiated human newborn infants, a retrospective study." <u>Journal Medical Libanais</u> <b>50</b> (1-2): 17-22.
	Laptook, A. R., R. J. Corbett, et al. Modest hypothermia provides partial neuroprotection when used for immediate resuscitation after brain ischemia. <u>Pediatr Res</u> 1997; 42(1): 17-23.
{ Simbruner, 1999 #228 }	Laptook, A. R., R. J. Corbett, et al. A limited interval of delayed modest hypothermia

<p>{Taylor, 2002 #226}</p>	<p>for ischemic brain resuscitation is not beneficial in neonatal swine. <u>Pediatr Res</u> 1999; 46(4): 383-9.</p>
<p>{The Hypothermia after Cardiac Arrest Study Group, 2002 #237}</p>	<p>Shankaran, S., A. Laptook, et al. Whole-body hypothermia for neonatal encephalopathy: animal observations as a basis for a randomized, controlled pilot study in term infants <u>Pediatrics</u> 2002 ; <b>110</b>(2 Pt 1): 377-85.</p>
<p>{Thoresen, 2001 #243}</p>	<p>Simbruner, G., C. Haberl, et al. Induced brain hypothermia in asphyxiated human newborn infants: a retrospective chart analysis of physiological and adverse effects. <u>Intensive Care Med</u> 1999; <b>25</b>(10): 1111-7.</p>
<p>{Thoresen, 2001 #244}</p>	<p>Taylor, D. L., H. Mehmet, et al Improved neuroprotection with hypothermia delayed by 6 hours following cerebral hypoxia-ischemia in the 14-day-old rat. <u>Pediatr Res</u> 2002; <b>51</b>(1): 13-9.</p>
<p>{Tooley, 2003 #242}</p>	<p>The Hypothermia after Cardiac Arrest Study Group Mild Therapeutic Hypothermia to Improve the Neurologic Outcome after Cardiac Arrest. <u>N Engl J Med</u> 2002; <b>346</b>(8): 549-556.</p>
<p>{Wagner, 2002 #230}</p>	<p>Thoresen, M., S. Satas, et al. Twenty-four hours of mild hypothermia in unседated newborn pigs starting after a severe global hypoxic-ischemic insult is not neuroprotective" <u>Pediatr Res</u> 2001; <b>50</b>(3): 405-11.</p>
<p>{Zhou, 2002 #224}</p>	<p>Thoresen, M., M. Simmonds, et al Effective selective head cooling during posthypoxic hypothermia in newborn piglets. <u>Pediatr Res</u> 2001; <b>49</b>(4): 594-9.</p>
<p>{Zhu, 2004 #236}</p>	<p>Tooley, J. R., S. Satas, et al Head cooling with mild systemic hypothermia in anesthetized piglets is neuroprotective. <u>Ann Neurol</u> 2003 <b>53</b>(1): 65-72.</p>
<p></p>	<p>Wagner, B. P., J. Nedelcu, et al. Delayed postischemic hypothermia improves long-term behavioral outcome after cerebral hypoxia-ischemia in neonatal rats. <u>Pediatr Res</u> 2002 ; <b>51</b>(3): 354-60.</p>
<p></p>	<p>Zhou, W. H., X. M. Shao, et al. Safety study of hypothermia for treatment of hypoxic-ischemic brain damage in term neonates. <u>Acta Pharmacologica Sinica</u> 2002; <b>23</b>(SUPPL): 64-68.</p>
<p></p>	<p>Zhu, C., X. Wang, et al. Post-ischemic hypothermia-induced tissue protection and diminished apoptosis after neonatal cerebral hypoxia-ischemia. <u>Brain Research</u> 2004; <b>996</b>(1): 67-75.</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.

**Akisu, M., A. Huseyinov, et al. (2003). "Selective head cooling with hypothermia suppresses the generation of platelet-activating factor in cerebrospinal fluid of newborn infants with perinatal asphyxia." Prostaglandins Leukotrienes & Essential Fatty Acids 69(1): 45-50.(LOE 7)**

**Abstract**

Hypoxic-ischemic encephalopathy (HIE) remains one of the most important neurologic complications in the newborn. Several experimental and clinical studies have shown that hypothermia is the most effective means known for protecting the brain against hypoxic-ischemic brain damage. Furthermore, recent data have suggested that platelet-activating factor (PAF) could play a pathophysiologically important role in the progression of hypoxic-ischemic brain injury. **Objectives** 1) To investigate the role of head cooling combined with minimal hypothermia in short-term outcome of infants with perinatal asphyxia 2) To examine the effect of head cooling combined with minimal hypothermia on **PAF concentrations in cerebrospinal fluid (CSF)** after hypoxic-ischemic brain injury. The group of asphyxiated infants (Group 1) consisted of 21 full-term (gestational age > 37 weeks). These infants were randomized and divided into either a standard therapy group (Group 1a; n = 10) or cooling group (Group 1b; n = 11). Head cooling combined with minimal hypothermia (rectal temperature 36.5-36[degrees]C) was started as soon as practicable after birth. The infants were cooled for 72 h and then were rewarmed at 0.5[degrees]C/h. The control group (Group 2) consisted of seven full-term infants and none of these infants showed any sign of asphyxia. To measure PAF concentration in CSF, CSF with lumbar puncture was collected into tubes immediately before the cooling (1-3 h after birth) and again after 36 h. **Results** No evidence of severe adverse events related to hypothermia was noted. In Group 1a, two infants died after 72 h of life; however, all newborn infants in Group 1b survived. Convulsion required treatment in three infants of standard therapy group (1a); none of the infants in Group 1b had clinical seizure activity. Abnormal EEG patterns were found in four infants of Group 1a; no EEG abnormalities were noted in Group 1b (P < 0.05). On admission (before cooling), PAF concentration in CSF of asphyxiated infants was found to be significantly higher when compared with that of control (P < 0.001). Mean PAF concentration before initiation of the study was similar in the two asphyxiated groups (Group 1a vs. 1b) (P > 0.05). Obtained PAF level in CSF after 36 h, showed a profound decline in cooling group of infants compared to Group 1a infants (P < 0.01). **Conclusion**, the present study suggests that cerebral cooling with minimal hypothermia started soon after birth has no severe adverse effects during 72-h cooling period and that short-term outcome of infants are encouraging. Our results also support the hypothesis PAF an important mediator in hypoxic-ischemic brain injury and demonstrate that head cooling combined with minimal hypothermia reduces the normal increase in PAF following hypoxic-ischemic brain injury in full-term infants.

**Comment** Although a randomized study the end points were side effects and the effect of cooling on CSF PAF concentrations. Moreover the study embraces very small numbers ( n=20).

Level of Evidence: 2  
Quality: Fair  
Evidence: Supportive

**Azzopardi, D., N. J. Robertson, et al. Pilot study of treatment with whole body hypothermia for neonatal encephalopathy. Pediatrics 2000 106(4): 684-94**

**Abstract**

**BACKGROUND:** There is extensive experimental evidence to support the investigation of treatment with mild hypothermia after birth asphyxia. However, clinical studies have been delayed by the difficulty in predicting long-term outcome very soon after birth and by concern about adverse effects of hypothermia. **OBJECTIVES:** The objectives of this study were to determine whether it is feasible to select infants with a bad neurological prognosis and to begin hypothermic therapy within 6 hours of birth, and to observe the effect of this therapy on relevant physiologic variables. **METHODS:** Sixteen newborn infants with clinical features of birth asphyxia (median cord blood pH: 6.74; range: 6.58-7.08) were assessed by amplitude integrated electroencephalography (aEEG), and mild whole body hypothermia was instituted within 6 hours of birth in the 10 infants with an aEEG prognostic of a bad outcome. Rectal temperature was maintained at 33.2 +/- (standard deviation).6 degrees C for 48 hours. Rectal and tympanic membrane temperature, blood pressure, heart rate, blood gases, blood lactate, full blood count, blood electrolytes, high and low shear rate viscosity, and coagulation studies were monitored during and after cooling. A preliminary assessment of neurological

outcome was made by repeated magnetic resonance imaging (MRI) and neurological examination. **RESULTS:** All infants selected to receive hypothermia developed convulsions and a severe encephalopathy. During 48 hours of hypothermia infants had prolonged metabolic acidosis (median pH: 7.30; base excess: -6.3 mmol x L(-1)), a high blood lactate (median lactate: 5.3 mmol x L(-1)) and low blood potassium levels (median value: 3.9 mmol x L(-1)). Hypothermia was associated with lower heart rate and higher mean blood pressure. However, these changes did not seem to be clinically relevant and no significant complication of hypothermia was encountered. Blood viscosity and coagulation studies were similar during and after cooling. Unusual MRI findings were noted in 3 infants: transverse sinus thrombosis with subsequent small cerebellar infarct; probable thrombosis in the straight sinus; and hemorrhagic cerebral infarction. Six of the 10 cooled infants had minor abnormalities only or normal follow-up neurological examination; 3 infants died and 1 had major abnormalities. None of the 6 infants with a normal aEEG developed severe neonatal encephalopathy or neurological sequel. **CONCLUSIONS:** After birth asphyxia infants can be objectively selected by aEEG and hypothermia started within 6 hours of birth in infants at high risk of developing severe neonatal encephalopathy. Prolonged mild hypothermia to 33 degrees C to 34 degrees C is associated with minor physiologic abnormalities. Further studies of both the safety and efficacy of mild hypothermia, including further neuroimaging studies, are warranted.

**Comments** Feasibility or pilot study demonstrating the safety of whole body cooling

Level of Evidence: 5  
Quality: Fair  
Evidence: Supportive

**Battin, M. R., J. A. Dezoete, et al. Neurodevelopmental outcome of infants treated with head cooling and mild hypothermia after perinatal asphyxia. Pediatrics 2001 107(3): 480-4. (LOE 3)**

**Abstract**

**OBJECTIVES:** To determine the neurodevelopmental outcome of infants treated with head cooling with systemic hypothermia after hypoxic-ischemic encephalopathy. **STUDY DESIGN:** Infants  $\geq 37$  weeks' gestation, who had an umbilical artery pH  $\leq 7.09$  or Apgar score  $\leq 6$  at 5 minutes, plus clinical encephalopathy. Infants with major congenital abnormalities were excluded. **TRIAL DESIGN:** Infants were allocated to either no cooling (rectal temperature =  $37.0 \pm 0.2$  degrees C, n = 15), or, sequentially, to head cooling accompanied by different levels of systemic hypothermia, including minimal cooling, rectal temperature 36.5 degrees C to 36 degrees C (n = 6), and mild cooling, to either 35.9 degrees C to 35.5 degrees C (n = 6),  $35 \pm 0.5$  degrees C (n = 6) or  $34.5 \pm 0.5$  degrees C (n = 7). Head cooling was accomplished by circulating cooled water through a coil of tubing wrapped around the head for up to 72 hours. Survivors were followed up with regular neurologic examination by a neonatologist until 18 months of age, then with blinded developmental testing using the revised Bayley Scales. **RESULTS:** A total of 40 term infants were enrolled from 2 to 5 hours after birth. The control and the cooled groups were not significantly different for gestation, birth weight, Apgar score, and initial pH. There were 6 early neonatal deaths (3 normothermic and 3 cooled), and 1 death in infancy associated with severe spastic cerebral palsy in a normothermic infant. Six normothermic, 1 minimally cooled, and 4 mildly cooled infants had early stage 1 encephalopathy; all but 1 had a good outcome. Among infants with early stage 2 or 3 encephalopathy, an adverse outcome was found in 4 of 9 normothermic infants (44%) and 4 of 5 minimally cooled infants (80%), whereas in the combined mildly cooled groups, an adverse outcome was found in 4 of 15 infants (26%, odds ratio 0.46 [0.08, 2.56] vs normothermia). **CONCLUSIONS:** The present study supports the safety of hypothermia, with no evidence of late adverse effects in any infant. Among infants with moderate to severe encephalopathy at enrollment, there was a tendency toward better outcome. These results emphasize the relatively wide range of outcomes using purely clinical criteria for enrollment. Therapeutic hypothermia should not be used outside of stringent, multicenter trials.

**Comment** Outcome study Sequential design-small numbers-safety study

Level of Evidence: 3  
Quality: Fair  
Evidence: Supportive

**Battin, M. R., J. Penrice, et al. Treatment of term infants with head cooling and mild systemic hypothermia (35.0 degrees C and 34.5 degrees C) after perinatal asphyxia. Pediatrics 2003 111(2): 244-51**

**Abstract**

**OBJECTIVE:** To assess the safety of selective head cooling in birth-asphyxiated term newborn infants while

maintaining the rectal temperature at 35.0 degrees C or 34.5 degrees C. **METHODS:** Twenty-six term infants with Apgar <or=6 at 5 minutes or cord/first arterial pH <7.1, plus evidence of encephalopathy, were studied. After parental consent had been obtained, 13 infants received selective head cooling with the rectal temperature maintained at 35.0 degrees C in 6 infants and at 34.5 degrees C in 7 infants. The remaining 13 infants were normothermic. Cooling was achieved by circulating water at 10 degrees C through a cap placed around the head. Rectal, fontanelle, and nasopharyngeal temperatures were monitored. **RESULTS:** One cooled infant died 2 days after rewarming, and 3 control infants died. Seizures occurred in 9 (69%) of 13 cooled infants and 5 (38%) of 13 control infants. Respiratory support within the first 72 hours of life was required in 10 of 13 infants in both the cooled and control groups. Three cooled infants and 1 control infant received nitric oxide for persistent pulmonary hypertension. During the same interval, 6 of the cooled infants and 4 of the control infants had episodes in which their blood pressure fell to <40 mm Hg; in 2 infants in each group, the lowest blood pressure was below 35 mm Hg. No requirement for volume expansion or increased inotropic support was seen in any infant during stepwise rewarming. All of the cooled infants demonstrated a fall in heart rate during cooling, but the rate was <80/min in only 2 cases and no infant had a rate <70/min. No infant demonstrated an abnormal rhythm or was clinically compromised by the change in heart rate. One infant cooled to a rectal temperature of 34.5 degrees C had a prolonged QT interval of 570 ms associated with a heart rate of 85/min on electrocardiogram aged 34 hours. This returned to normal after rewarming. Platelet counts below 150 x 10<sup>9</sup>/L, hypoglycemia below 2.6 mmol/L, and highest creatinine were not statistically different between cooled and control infants. Positive precooling blood cultures were found in 1 cooled and 1 control infant. The mean cap water input temperature used during cooling was 10 +/- 1 degrees C. During active cooling, the mean difference between rectal and nasopharyngeal temperature was 1.4 degrees C in the infants who were not receiving respiratory support, but this gradient could not be measured in those who were receiving respiratory support that involved delivery of warmed gases to the nasopharynx. **CONCLUSIONS:** This study suggests that selective head cooling combined with mild systemic hypothermia of 34.4 degrees C or 35.0 degrees C is a stable, well-tolerated method of reducing cerebral temperature in term newborn infants after perinatal asphyxia.

**Comment** Non randomized study with control group. A safety study

Level of Evidence: 3

Quality: Fair

Evidence: Supportive

**Bernard, S. A., T. W. Gray, et al. (2002). "Treatment of Comatose Survivors of Out-of-Hospital Cardiac Arrest with Induced Hypothermia." N Engl J Med 346(8): 557-563. (LOE 7)**

**Abstract**

Background Cardiac arrest outside the hospital is common and has a poor outcome. Studies in laboratory animals suggest that hypothermia induced shortly after the restoration of spontaneous circulation may improve neurologic outcome, but there have been no conclusive studies in humans. In a randomized, controlled trial, we compared the effects of moderate hypothermia and normothermia in patients who remained unconscious after resuscitation from out-of-hospital cardiac arrest. Methods The study subjects were 77 patients who were randomly assigned to treatment with hypothermia (with the core body temperature reduced to 33{degrees}C within 2 hours after the return of spontaneous circulation and maintained at that temperature for 12 hours) or normothermia. The primary outcome measure was survival to hospital discharge with sufficiently good neurologic function to be discharged to home or to a rehabilitation facility. Results The demographic characteristics of the patients were similar in the hypothermia and normothermia groups. Twenty-one of the 43 patients treated with hypothermia (49 percent) survived and had a good outcome -- that is, they were discharged home or to a rehabilitation facility -- as compared with 9 of the 34 treated with normothermia (26 percent, P=0.046). After adjustment for base-line differences in age and time from collapse to the return of spontaneous circulation, the odds ratio for a good outcome with hypothermia as compared with normothermia was 5.25 (95 percent confidence interval, 1.47 to 18.76; P=0.011). Hypothermia was associated with a lower cardiac index, higher systemic vascular resistance, and hyperglycemia. There was no difference in the frequency of adverse events. Conclusions Our preliminary observations suggest that treatment with moderate hypothermia appears to improve outcomes in patients with coma after resuscitation from out-of-hospital cardiac arrest.

**Comment** Adult study with important protective effects of hypothermia

Level of Evidence: 7

Quality: Good

Evidence: Supportive

**Bona, E., H. Hagberg, et al. Protective effects of moderate hypothermia after neonatal hypoxia-ischemia: short- and long-term outcome. Pediatr Res 1998;43(6): 738-45.**

### **Abstract**

We have previously shown that mild hypothermia applied after hypoxia-ischemia in newborn piglets and rats reduces brain injury evaluated 3-7 d after the insult. The aim of the present study was to assess the neuroprotective efficacy of hypothermia with respect to short- (neuropathology) and long-term (neuropathology and sensorimotor function) outcome after hypoxia-ischemia in 7-d-old rats. One hundred fourteen animals from 13 litters survived either 1 or 6 wk after a hypoxic-ischemic insult. The animals were randomized to either 1) normothermic recovery for the whole 1- or 6-wk period or 2) cooling to a rectal temperature of 32.0 degrees C for the first 6 h followed by normothermic recovery with the dam. Hypothermia offered a uniform protection of 27, 35, 28, and 25% in cerebral cortex, hippocampus, basal ganglia, and thalamus, respectively, in the 1-wk survivors (n = 32). The corresponding values for the 6-wk survivors (n = 61) were 22, 28, 37, and 35%. There was a significant correlation between sensorimotor performance and infarct volume ( $r = 0.66$ ;  $p < 0.001$ ). However, the sensorimotor function was not significantly improved by hypothermia if all animals were included, but in female pups the total functional score was higher in the hypothermia group ( $150 \pm 35$  versus  $100 \pm 34$ ,  $p < 0.0007$ ) which corresponded to a marked (51%) reduction of the neuropathology score in this subgroup. **This is the first neonatal study to show a long-term histopathologic protection of the brain after posthypoxic hypothermia.**

**Comment** Well conducted animal study with histopathologic data

Level of Evidence: 6

Quality: Good

Evidence: Supportive

### **Compagnoni, G., L. Pogliani, et al. Hypothermia reduces neurological damage in asphyxiated newborn infants. Biol Neonate 2002; 82(4): 222-7.**

#### **Abstract**

**BACKGROUND:** Perinatal asphyxia remains one of the most devastating neurologic processes. There is experimental and clinical evidence that cerebral cooling may suppress the biochemical cascades leading to delayed cerebral damage. **OBJECTIVE:** To determine if hypothermia started soon after delivery reduces cerebral damage in term infants. **Methods:** Retrospective chart analysis with historical controls. Ten asphyxiated newborns treated with hypothermia between October 1998 and October 1999 were compared to 11 asphyxiated newborns admitted from September 1997 to September 1998. Characteristics at birth of infants of the two groups (control and hypothermia) were comparable. After obtaining parental consent, whole-body hypothermia was induced before the 6th hour of life by placing a cold blanket (Polar Air, Augustine Medical Inc., model 600) around the body of the patients. Rectal temperature was maintained between 32 and 34 degrees C for 72 h. Outcome was assessed by neurological evaluation at birth and every 3 months up to the 12th month. Brain MRI was performed in the 2nd month. **Results** We had no evidence of severe adverse events related to hypothermia. In the hypothermic group there was a significant ( $p < 0.05$ ) reduction of major neurologic abnormalities at follow-up and abnormal MRI findings. **CONCLUSIONS:** Hypothermia appears to be safe. Our results on morphological damage evaluated by brain MRI and neurological outcome are encouraging: randomized controlled trials are needed to confirm this experience.

**Comments** Small numbers, historical controls. No side effects of hypothermia

Level of Evidence: 4

Quality: Fair

Evidence: Supportive

### **Debillon, T., P. Daoud, et al. Whole-body cooling after perinatal asphyxia: A pilot study in term neonates. Developmental Medicine & Child Neurology 2003; 45(1): 17-23.**

#### **Abstract**

In order to test the practicability and safety of whole-body cooling in term neonates with moderate-to-severe hypoxic-ischaemic encephalopathy (HIE) and to report outcomes, a prospective pilot study was carried out in 25 term infants (median postmenstrual age 38 weeks, range 36 to 41 weeks; 20 males, five females). Whole-body cooling, to a target core temperature of 33 to 34[degrees]C, started within 6 hours of birth and was maintained for 72 hours. Of the 25 newborn infants (19 Sarnat II and six Sarnat III, 18 outborn), 18 survived, including 13 (72%) with normal cerebral signal by MRI. Temperature instability occurred during cooling in 15 infants, but neither severe haemodynamic instability nor renal failure was seen. Thrombocytopenia developed in 12 infants, including seven with biological disseminated intravascular coagulation. One patient had hypoxaemia with right-to-left shunting through the ductus arteriosus, and seven had limited meningeal or subdural bleeding. Whole-body cooling is feasible in term neonates, with no life-threatening adverse events. Improvements are needed to obtain stable hypothermia for 72 hours.

**Comments** Small numbers, serial patients without a control group. Problems in maintaining temperature-

thrombocytopenia developed in 12 infants

Level of Evidence: 5

Quality: Fair

Evidence: Supportive but possible side effects

**Gunn, A. J., T. R. Gunn, et al. (1997). "Dramatic neuronal rescue with prolonged selective head cooling after ischemia in fetal lambs." Journal of Clinical Investigation 99(2): 248-256.**

**Abstract**

Hypothermia has been proposed as a neuroprotective strategy. However, short-term cooling after hypoxia-ischemia is effective only if started immediately during resuscitation. The aim of this study was to determine whether prolonged head cooling, delayed into the late postinsult period, improves outcome from severe ischemia. Unanesthetized near-term fetal sheep were subject to 30 min of cerebral ischemia. 90 min later they were randomized to either cooling (n = 9) or sham cooling (n = 7) for 72 h. Intrauterine cooling was induced by a coil around the fetal head, leading initially to a fall in extradural temperature of 5-10 [degree]C, and a fall in esophageal temperature of 1.5-3 [degree]C. Cooling was associated with mild transient systemic metabolic effects, but not with hypotension or altered fetal heart rate. Cerebral cooling reduced secondary cortical cytotoxic edema (P < 0.001). After 5 d of recovery there was greater residual electroencephalogram activity (-5.2 +/- 1.6 vs. -15.5 +/- 1.5 . dB, P < 0.001) and a dramatic reduction in the extent of cortical infarction and neuronal loss in all regions assessed (e.g., 40 vs. 99% in the parasagittal cortex, P < 0.001). Selective head cooling, maintained throughout the secondary phase of injury, is noninvasive and safe and shows potential for improving neonatal outcome after perinatal asphyxia.

**Comments** Seminal large animal study demonstrating the effectiveness of hypothermia in reducing brain injury

Level of Evidence: 6

Quality: Excellent

Evidence: Supportive

**Gunn, A. J., T. R. Gunn, et al. (1998). "Neuroprotection with prolonged head cooling started before postischemic seizures in fetal sheep." Pediatrics 102(5): 1098-1106.**

**Abstract**

**Objective.** Cerebral hypothermia has been shown to reduce damage from experimental hypoxiaischemia if started shortly after reperfusion. However, in the newborn infant it may not be feasible to determine prognosis so soon after exposure to asphyxia. The aim of this study was to determine whether head cooling, delayed until shortly before the onset of postasphyxial seizure activity, is neuroprotective. **Methods.** Unanesthetized near-term fetal sheep in utero were subjected to 30 minutes of cerebral ischemia. Later, at 5.5 hours, they were randomized to either cooling (n = 7) or sham cooling (n = 10) for 72 hours. Intrauterine cooling was induced by circulating cold water through a coil around the fetal head. The water temperature was titrated to reduce fetal extradural temperature from 39.1 +/- 0.1 [degree]C to between 30 [degree]C and 33 [degree]C, while maintaining esophageal temperature >37 [degree]C. **Results.** Cerebral cooling suppressed the secondary rise in cortical impedance (a measure of cytotoxic edema), but did not prevent delayed seizures, 8 to 30 hours after ischemia. Transient metabolic changes including increased plasma lactate and glucose levels were seen with a moderate sustained rise in blood pressure. This severe cerebral insult resulted in depressed residual parietal electroencephalographic activity after 5 days recovery (-14.2 +/- 1.5 decibels), associated with a watershed distribution of neuronal loss (eg, 94 +/- 4% in parasagittal cortex and 77 +/- 4% in the lateral cortex). Hypothermia was associated with better recovery of electroencephalographic activity (- 8.9% +/- 1.8 decibels) and substantially reduced neuronal loss in the parasagittal cortex (46 +/- 13%), the lateral cortex (9 +/- 4%), and other regions except the cornu ammonis sectors 1 and 2 of the hippocampus. **Conclusions. Delayed selective head cooling begun before the onset of postischemic seizures and continued for 3 days may have potential to significantly improve the outcome of moderate to severe hypoxic-ischemic encephalopathy.**

**Comments** Important timing study in a large animal model suggesting implementation of an intervention prior to six hours

Level of Evidence: 6

Quality: Good

Evidence: Supportive

**Gunn, A. J., L. Bennet, et al. (1999). "Cerebral hypothermia is not neuroprotective when started after postischemic seizures in fetal sheep." Pediatr Res 46(3): 274-80.**

**Abstract**

Prolonged cerebral hypothermia is neuroprotective if started within a few hours of hypoxia-ischemia. However, delayed seizure activity is one of the major clinical indicators of an adverse prognosis after perinatal asphyxia. The aim of this study was to determine whether head cooling delayed until after the onset of postasphyxial seizures may still be neuroprotective. Unanesthetized near-term fetal sheep in utero received 30 min of cerebral ischemia induced by bilateral carotid artery occlusion. Eight and one-half hours later, they received either cooling (n = 5) or sham cooling (n = 13) until 72 h after the insult. Intrauterine cooling, induced by circulating cold water through a coil around the fetal head, was titrated to reduce fetal extradural temperature from 39.4±0.1 degrees C to between 30 and 33 degrees C. Cerebral ischemia led to the delayed development of intense epileptiform activity from 6 to 8 h postinsult, followed by a marked secondary rise in cortical impedance (a measure of cytotoxic edema) and in carotid blood flow. Cerebral cooling markedly attenuated the secondary rise in impedance and reduced carotid blood flow (p < 0.001). After 5 d recovery, there was no significant difference in loss of parietal EEG activity relative to baseline in the hypothermia compared with the control group (-12.5±1.4 versus -15.2±1.2 dB, mean ± SEM, NS) or in parasagittal cortical neuronal loss (82±9 versus 90±5%, NS). **Conclusion, Delayed prolonged head cooling begun after the onset of post-ischemic seizures was not neuroprotective. These data highlight the importance of intervention in the latent phase, after reperfusion but before the onset of secondary injury.**

**Comments** Important timing study showing no effect with delayed intervention

Level of Evidence: 6

Quality: Good

Evidence: Negative study

**Gunn, A. J., P. D. Gluckman, et al. (1998). "Selective head cooling in newborn infants after perinatal asphyxia: A safety study." Pediatrics 102(4 I): 885-892.**

**Abstract**

**Objective** To determine the practicality and safety of head cooling with mild or minimal systemic hypothermia in term neonates with moderate to severe hypoxic-ischemic encephalopathy. **Methods.** Study group infants ≤37 weeks' gestation, who had an umbilical artery pH ≤7.09 or Apgars ≤6 at 5 minutes, plus evidence of encephalopathy. Infants with major congenital abnormalities were excluded. **Trial Design.** Infants were randomized to either no cooling (controls; rectal temperature = 37.0 ± 0.2 [degree]C, n = 10) or sequentially, either minimal systemic cooling (rectal temperature = 36.3 ± 0.2 [degree]C, n = 6) or mild systemic cooling (rectal temperature = 35.7 ± 0.2 [degree]C, n = 6). Head cooling was accomplished by circulating water at 10 [degree]C through a coil of tubing wrapped around the head for up to 72 hours. All infants were warmed by servo-controlled overhead heaters to maintain the allocated rectal temperature. The rectal, fontanel, and nasopharyngeal temperatures were continuously monitored. **Results.** From January 1996 to October 1997, 22 term infants were randomized from 2 to 5 hours after birth. All infants showed a metabolic acidosis at delivery, with similar umbilical artery pH in the control group (mean ± standard deviation, 6.79 ± 0.25), minimal cooling group (6.98% ± 0.21), and mild cooling group (6.93 ± 0.11), and depressed Apgar scores at 5 minutes in the control group (4.5 ± 2), minimal cooling group, (4.7 ± 2) and mild cooling group (6.0 ± 1). In the mild-cooled infants, the nasopharyngeal temperature was 34.5 [degree]C during cooling, 1.2 [degree]C lower than the rectal temperature. This gradient narrowed to 0.5 [degree]C after cooling was stopped. No adverse effects because of cooling were observed. No infants developed cardiac arrhythmias, hypotension, or bradycardia during cooling. Thrombocytopenia occurred in 2 out of 10 controls, 2 out of 6 minimal cooling infants, and 1 out of 6 mild cooling infants. Hypoglycemia (glucose <2.6 mM) was seen on at least one occasion in 2 out of 10 controls, 4 out of 6 minimal cooling infants, and 1 out of 6 mild cooling infants. Acute renal failure occurred in all infants. The metabolic acidosis present in all infants at the time of enrollment into the study progressively resolved despite cooling, even in the mild hypothermia group. **Conclusions.** Mild selective head cooling combined with mild systemic hypothermia in term newborn infants after perinatal asphyxia is a safe and convenient method of quickly reducing cerebral temperature with an increased gradient between the surface of the scalp and core temperature. The safety of mild hypothermia with selective head cooling is in contrast with the historical evidence of adverse effects with greater depths of whole-body hypothermia. This safety study and the strong experimental evidence for improved cerebral outcome justify a multicenter trial of selective head cooling for neonatal encephalopathy in term infants.

**Comment** While a randomized study it was in essence a **pilot study** with a randomized but sequential design. With minimal hypothermia (rectal temperature 35.7 °C, no adverse effects were noted

Level of Evidence: 2  
Quality: Fair-  
Evidence: Supportive study

**Haaland, K., E. M. Loberg, et al. Posthypoxic hypothermia in newborn piglets. Pediatr Res 1997 41(4 Pt 1): 505-12.**

**Abstract**

The purpose of this study was to determine whether mild hypothermia after a moderate hypoxic-ischemic insult reduces the extent of brain damage. Hypoxia was achieved in newborn piglets (n = 24; age, 14-72 h) by abrupt reduction of the inspired oxygen concentration (FiO<sub>2</sub>) to the maximum concentration (approximately 6%) giving low amplitude (< 7.0 microV) EEG. FiO<sub>2</sub> was temporarily increased if heart rate, blood pressure, or end expiratory partial pressure of alveolar CO<sub>2</sub> (PACO<sub>2</sub>) were markedly reduced. This intermittently resulted in EEG amplitude greater than 7 microV, the EEG traces were therefore later examined to determine the duration of low amplitude EEG. After 45 min of hypoxia, the animals were randomized to normothermia (39 degrees C) or hypothermia (35 degrees C) for 3 h. Hypothermia was achieved by applying packs containing ice water. Neurologic assessments and EEG recordings were performed regularly until 3 d when the brains were perfusion fixed. Histologic damage in cortex/white matter, cerebellum, hippocampus, basal ganglia, and thalamus was graded by a pathologist blind to treatment allocation. We found that the severity of brain damage (by histopathologic and neurologic evaluation) was not significantly different when the piglets were normothermic after hypoxia compared with the group made hypothermic. Increased duration of low amplitude EEG and seizure activity were associated with increased damage. When controlling for duration of hypoxia and excluding seizures, piglets undergoing hypothermia had approximately 50% less severe histopathologic damage in cortex/white matter, cerebellum, and hippocampus than those kept normothermic. Thalamus and basal ganglia had no or minor damage. It was concluded that there was no general beneficial effect of postinsult hypothermia. However, when controlling for the duration of the insult and occurrence of seizures, hypothermia reduced the severity of brain damage. **This indicates a significant neuroprotective effect of 3 h of mild hypothermia on moderate, but not severe, hypoxic-ischemic insults.**

Level of Evidence: 6  
Quality: Fair-  
Evidence: Supportive study

**Horan, M., S. Ichiba, et al. A pilot investigation of mild hypothermia in neonates receiving extracorporeal membrane oxygenation (ECMO). Journal of Pediatrics 2004144(3): 301-308.**

**Abstract**

**Objective:** To investigate the **safety and feasibility** of using mild hypothermia in neonates receiving extracorporeal membrane oxygenation (ECMO). Study design: A **prospective, nonrandomized** pilot study of 25 neonates referred for ECMO. Whole body cooling was achieved by adjustment of the temperature of the extracorporeal circuit water bath. Five groups (N = 5 per group) were each studied for the first 5 days of ECMO. The first group was maintained at 37[degrees]C throughout the study period. Subsequent groups were cooled to 36[degrees]C, to 35[degrees]C, and, finally, to 34[degrees]C, respectively, for 24 hours and the final group to 34[degrees]C for 48 hours before being rewarmed to 37[degrees]C. Patients were carefully assessed clinically and biologically. In addition to routine laboratory tests, cytokines (IL-6 and IL-8), complement (C3a), and molecular markers of coagulation (thrombin/antithrombin III [TAT], antithrombin III, and plasmin-[alpha]2plasminogen) were measured. **Results:** No major clinical or circuit problems were noted during cooling or rewarming. In particular, there were no problems of bleeding or cardiac arrhythmia. No significant difference was found between groups in terms of molecular markers of coagulation, complement, cytokines, and platelet transfusions. **Conclusions:** Applying mild hypothermia (34[degrees]C) for 24 or 48 hours to neonates receiving ECMO is both feasible and safe.

Level of Evidence: 7  
Quality: Fair  
Evidence: Supportive study

**Kilani, R. A. (2002). "The safety and practicality of selective head cooling in asphyxiated human newborn infants, a retrospective study." Journal Medical Libanais 50(1-2): 17-22.**

**Abstract**

**Objective** To evaluate the practicality and safety of selective head cooling in asphyxiated human newborn infants. **Methods** Retrospective chart analysis of asphyxiated neonates: During a period of 13 months (1st June 1998 to 30 June

1999) n=14 newborns (10 mild and 4 moderate PHIE) were managed by selective head-cooling (mean GA 38.8 +/- 2.3) and 12 newborns (9 mild and 3 moderate PHIE) were managed conservatively without head cooling and served as controls (mean GA 39.1 +/- 1.6). **Selective head cooling** was accomplished by **applying cool-packs** to the parieto-temporal regions. **Results** There were no significant differences in the perinatal characteristics of the two groups. The mean scalp temperature of 33.8 +/- 0.4 [degrees]C (28.7-36.5 [degrees]C) was lower than the mean body temperature of 35.8 +/- 0.2 [degrees]C (32.2-37.0 [degrees]C) in the study group during the cooling period, compared to a mean body temperature of 36.7 +/- 0.2 [degrees]C (36.1-37.3 [degrees]C) in the control group during the study period. There were no significant differences in the incidence of possible adverse effects between the two groups of infants. No infants developed cardiac arrhythmia, bradycardia, pulmonary edema or hemorrhage, metabolic acidosis, hypoglycemia, hypokalemia, NEC, systemic infection, thrombocytopenia, polycythemia, or cavernous sinus thrombosis during cooling. **Conclusions:** Our data demonstrates that selective head cooling is practical and effective in keeping a gradient between the scalp and body temperature with no observed systemic side effects.

Level of Evidence: 5

Quality: Fair-

Evidence: Supportive study

**Laptook, A. R., R. J. Corbett, et al. Modest hypothermia provides partial neuroprotection when used for immediate resuscitation after brain ischemia. Pediatr Res 1997 42(1): 17-23.**

**Abstract**

Intrascemic reduction in temperature of 2-3 degrees C (modest hypothermia) has been demonstrated to provide partial neuroprotection in neonatal animals. This investigation determined if modest hypothermia initiated immediately after brain ischemia provides neuroprotection. Piglets were studied with rectal temperature maintained during the 1st h after 15 min of brain ischemia at either 38.3 +/- 0.3 degrees C (normothermia, n = 11) or at 35.8 +/- 0.5 degrees C (modest hypothermia, n = 11). The severity of brain ischemia was similar between groups as indicated by equivalent reduction in mean blood pressure (90 +/- 15 to 24 +/- 3 versus 92 +/- 13 to 26 +/- 3 mm Hg), and changes in cerebral metabolites and intracellular pH (pH(i)) measured by magnetic resonance spectroscopy (beta-nucleoside triphosphate = 44 +/- 9 versus 42 +/- 18% of control, control = 100%, pH(i): 6.25 +/- .15 versus 6.24 +/- 0.22 for normothermic and modestly hypothermic groups, respectively). In the first 90 min after ischemia, there were no differences between groups in the duration and extent of brain acidosis, and relative concentrations of phosphorylated metabolites. Categorical assessment of neurobehavior was evaluated at 72 h postischemia (n = 16), or earlier if an animal's condition deteriorated (n = 6). Postischemic hypothermia was associated with less severe stages of encephalopathy compared with normothermia (p = 0.05). Histologic neuronal injury was assessed categorically in 16 brain regions, and postischemic hypothermia resulted in less neuronal injury in temporal (p = 0.024) and occipital (p = 0.044) cortex at 10 mm beneath the cortical surface, and in the basal ganglia (p = 0.038) compared with that in normothermia. Modest hypothermia for 1 h immediately after brain ischemia provides partial neuroprotection and may represent an adjunct to resuscitative strategies.

Level of Evidence: 6

Quality: Good

Evidence: Supportive study

**Laptook, A. R., R. J. Corbett, et al. A limited interval of delayed modest hypothermia for ischemic brain resuscitation is not beneficial in neonatal swine. Pediatr Res 1999 46(4): 383-9.**

**Abstract**

This investigation determined if a short interval of modest hypothermia (1 h) initiated 30 min after brain ischemia provided neuroprotection. The rationale for the time and duration of brain cooling reflects the likelihood that the implementation of neuroprotective strategies will occur at an interval shortly after ischemia, and that long-term maintenance of normothermia is a cornerstone of neonatal stabilization. Studies were performed in 22 ventilated neonatal mini-swine in a superconducting magnet to obtain 31P magnetic resonance spectra. After a control period all animals underwent 15 min of global brain ischemia and were maintained normothermic for the first 30 min post-ischemia. In one group of 11 swine normothermia was continued. In the other group of 11 swine, modest hypothermia was initiated at 30 min post-ischemia, continued for 1 h and followed by resumption of normothermia. Animals were subsequently weaned from ventilator support, removed from the magnet, and underwent neurobehavioral and histologic assessment at 72 h post-ischemia. Both groups had similar severity of ischemia, as indicated by identical changes in arterial blood pressure and pH, alterations in brain beta-nucleotide triphosphate (% of control where control = 100%, 32

+/- 28 vs 27 +/- 26% for normothermic and hypothermic groups, respectively), and the extent of intraschemic brain acidosis (6.13 +/- 0.19 vs 6.14 +/- 0.14 for normothermic and hypothermic groups, respectively). In both groups the distribution of stages of encephalopathy were the same: 1 normal and 10 abnormal (4 mild, 2 moderate, and 4 severe) normothermic, and, 3 normal and 8 abnormal (4 mild, 2 moderate, and 2 severe) hypothermic animals. There was no difference in the extent of neuronal injury between groups. **We conclude that a 1-h interval of modest hypothermia initiated at 30 min post-ischemia does not confer neuroprotection.**

Level of Evidence: 6

Quality: Good

Evidence: Negative

**Shankaran, S., A. Laptook, et al. Whole-body hypothermia for neonatal encephalopathy: animal observations as a basis for a randomized, controlled pilot study in term infants. Pediatrics 2002; 110(2 Pt 1): 377-85.**

**Abstract**

**OBJECTIVE:** Modest reduction in brain temperature is a promising therapy to reduce brain damage after neonatal encephalopathy as a result of acute perinatal asphyxia. The efficacy of modest hypothermia may in part be dependent on the stability of the desired brain temperature. The objective of this study was 1) to evaluate **in newborn animals** a commercially available cooling system (Blanketrol II Hyperthermia-Hypothermia system) to control brain temperature during whole-body hypothermia and 2) to use the results of the animal experiments to perform a pilot study evaluating the feasibility of whole-body hypothermia as a neuroprotective therapy for newborns with encephalopathy at birth.

**METHODS:** In the animal investigation, 3 miniature swine were instrumented and ventilated, and temperature probes were placed in the esophagus and the brain (1 cm and 2 cm beneath the parietal cortical surface and the dura). Body cooling was achieved using the automatic control mode (servo) of the cooling system. In the human investigation, 19 term infants with moderate or severe encephalopathy were randomized to either normothermia (n = 10) or hypothermia (n = 9) within 6 hours of birth. Whole-body hypothermia was achieved using the hyperthermia-hypothermia cooling system with servo control of esophageal temperature to 34.5 degrees C for 72 hours followed by slow rewarming.

**RESULTS:** In the animal investigation, body cooling with the animal lying on a single blanket resulted in rapid cooling of the body within 90 minutes. Repetitive cyclical swings in esophageal temperature of 1.7 +/- 0.2 degrees C (mean +/- standard deviation) around the set point of 33.5 degrees C were reduced to 0.7 +/- 0.2 degrees C when a second, larger blanket was attached and suspended. Esophageal temperature was a good marker of deep brain temperature (esophageal to 2-cm brain difference: 0.1 +/- 0.3 degrees C). In the human investigation, the infants were randomized at 4.1 +/- 1.3 hours (mean +/- standard deviation) after birth. Age at randomization was similar in the 2 groups. Cooling was initiated at an average age of 5.3 hours. Target temperature of 34.5 degrees C was achieved within 30 minutes and remained constant throughout the intervention period. Heart rate decreased to 108 +/- 14 beats per minute (bpm) at 60 minutes and remained between 115 and 130 bpm for the duration of cooling compared with 130 to 145 bpm in the normothermia group. Blood pressure was similar in the 2 groups. No adverse events occurred during 72 hours of cooling. The mortality rate and frequency of persistent pulmonary hypertension, renal failure, hepatic dysfunction, and need for pressor support were similar in both groups. **CONCLUSIONS:** Animal studies showed that a simple modification of a commercially available cooling system (2 blankets attached, subject lying on 1 and the second hanging freely) results in stable core body and brain temperature when used in the automatic control mode. The pilot study in term infants with encephalopathy using this cooling system demonstrates feasibility of initiating whole-body hypothermia at <6 hours of age to a constant esophageal temperature using servo control and provides no evidence that hypothermia involved greater hazard than benefit

**Comment** Safety study in animals (n=3) and term infants (n=19) who were randomized to modest hypothermia versus normothermia. This study was designed to assess the feasibility of using whole body cooling and for preliminary safety issues.

Level of Evidence: 2

Quality: Fair

Evidence: Supportive study

**Simbruner, G., C. Haberl, et al. Induced brain hypothermia in asphyxiated human newborn infants: a retrospective chart analysis of physiological and adverse effects. Intensive Care Med 1999; 25(10): 1111-7.**

**(LOE 4)**

**Abstract**

**OBJECTIVE:** To assess the physiological effects and adverse side-effects of induced hypothermia in asphyxiated

newborn infants as a base for future controlled, randomized trials. **DESIGN:** Retrospective chart analysis with historical controls. **SETTING:** Tertiary neonatal intensive care unit of the University of Cape Town, South Africa. **PATIENTS:** Twenty-one asphyxiated newborns treated with induced hypothermia between September 1997 and February 1998 were compared to 15 asphyxiated newborn infants admitted during March to August 1997. The two groups of infants did not differ in patient characteristics or severity of asphyxia (comparison group vs hypothermia group: Apgar at 5 min 5.3 +/- 3.1 vs 5.2 +/- 2.3; base deficit 15.6 +/- 6.3 vs 11.5 +/- 7.2 and Thompson neurological score 10.1 +/- 4.0 vs 9.1 +/- 3.6). **Methods:** Hypothermia was induced by placing a cap formed from coolpacks, at a temperature of about 10 degrees C, around the head of asphyxiated newborn infants to maintain the nasopharyngeal temperature between 34 and 35 degrees C. Hypothermia was maintained for 3 days. **Results:** In the comparison group 4/15 infants died and in the hypothermia group 4/21 died. Hypothermia was induced at a median of 6.0 h (range 45 min to 53 h) post-partum, maintained for an average of 80 h (median 77.5 h, range 22 to 185 h) and resulted in an average nasopharyngeal temperature of 34.6 +/- 0.5 degrees C. Hypothermia reduced abdominal skin temperature from 36.3 +/- 0.5 degrees C to 35.1 +/- 0.35 degrees C (p = 0.0001), heart rate from 139 +/- 21 to 121 +/- 13 beats/min (p < 0.0001) and respiratory rate from 67 +/- 11 to 56 +/- 9 breaths/min (p = 0.005). Neither episodes of bradycardia nor dysrhythmias, apnea, clinical signs of bleeding diathesis in the hypothermia group nor differences in the frequency of hypoglycaemia and urinary output, blood in urine or tracheal secretion between the two groups were observed. In the survivors the neurological score, assessed at day 2 and day 5, fell from 10.9 +/- 3.5 to 8.1 +/- 4.5 in the hypothermia group and rose from 8.1 +/- 2.5 to 9.0 +/- 3.1 in the comparison group (p = 0.003). **CONCLUSIONS:** Adverse effects of mild hypothermia induced for 3 days in asphyxiated newborns were significantly less than expected from previous reports on neonates with accidental hypothermia.

**Comment** Non randomized study and using asphyxiated non cooled babies as controls-the latter poorly defined. Using the method of cool caps, no side effects were noted

Level of Evidence: 4

Quality: Fair

Evidence: Supportive study

**Taylor, D. L., H. Mehmet, et al. Improved neuroprotection with hypothermia delayed by 6 hours following cerebral hypoxia-ischemia in the 14-day-old rat. Pediatr Res 2002; 51(1): 13-9.**

**Abstract**

Since hypothermia may be a potential treatment for perinatal cerebral hypoxic-ischemic injury, we used an established neonatal model of hypoxia-ischemia to determine the time after injury at which cooling had the best protective effect. Fourteen-day-old Wistar rats were subjected to right carotid artery ligation and hypoxia (8% O<sub>2</sub>) for 90 min. Immediately at the end of hypoxia (defined as 0h), animals were either maintained at normal body temperature until sacrifice (normothermia) or subjected to hypothermia. In a preliminary study, the effects of a reduction in temperature and the duration of such cooling were investigated; animals were cooled (until brain temperature reached 33 degrees C or 30 degrees C) for 2, 4, or 6 h commencing immediately after hypoxia. In a second study, animals were cooled (brain temperature 30 degrees C) for 6 h commencing at either 0, 2, 4, or 6 h after the end of hypoxia. Sham-operated animals were used as controls. Twenty-four hours after hypoxia-ischemia, cerebral energy metabolism was measured by phosphorus magnetic resonance spectroscopy, and at 5 d cerebral infarction was measured by planimetry. In normothermic animals the ratio of phosphocreatine/inorganic phosphate (PCr/Pi) had fallen markedly 24 h following hypoxia-ischemia. In contrast, animals cooled between 6 and 12 h displayed high PCr/Pi ratios similar to those in control animals. Similarly, after 5 d, infarct area was significantly reduced only in animals cooled between 6 and 12 h after injury. These results indicate that cooling between 6 and 12 h after hypoxia-ischemia is more effective in reducing cerebral injury than other cooling regimes and suggest that the physiologic events during this period are critical for understanding cerebral infarction.

Level of Evidence: 6

Quality: Fair

Evidence: Supportive study

**The Hypothermia after Cardiac Arrest Study Group ( Mild Therapeutic Hypothermia to Improve the Neurologic Outcome after Cardiac Arrest. N Engl J Med 2002; 346(8): 549-556.**

**Abstract**

Background Cardiac arrest with widespread cerebral ischemia frequently leads to severe neurologic impairment. We studied whether mild systemic hypothermia increases the rate of neurologic recovery after resuscitation from cardiac arrest due to ventricular fibrillation. Methods In this multicenter trial with blinded assessment of the outcome, patients

who had been resuscitated after cardiac arrest due to ventricular fibrillation were randomly assigned to undergo therapeutic hypothermia (target temperature, 32{degrees}C to 34{degrees}C, measured in the bladder) over a period of 24 hours or to receive standard treatment with normothermia. The primary end point was a favorable neurologic outcome within six months after cardiac arrest; secondary end points were mortality within six months and the rate of complications within seven days. Results Seventy-five of the 136 patients in the hypothermia group for whom data were available (55 percent) had a favorable neurologic outcome (cerebral-performance category, 1 [good recovery] or 2 [moderate disability]), as compared with 54 of 137 (39 percent) in the normothermia group (risk ratio, 1.40; 95 percent confidence interval, 1.08 to 1.81). Mortality at six months was 41 percent in the hypothermia group (56 of 137 patients died), as compared with 55 percent in the normothermia group (76 of 138 patients; risk ratio, 0.74; 95 percent confidence interval, 0.58 to 0.95). The complication rate did not differ significantly between the two groups.

Conclusions In patients who have been successfully resuscitated after cardiac arrest due to ventricular fibrillation, therapeutic mild hypothermia increased the rate of a favorable neurologic outcome and reduced mortality

**Comment**     **Seminal study in adults**

Level of Evidence: 7

Quality: Excellent

Evidence: Supportive study

**Thoresen, M., S. Satas, et al. Twenty-four hours of mild hypothermia in unsedated newborn pigs starting after a severe global hypoxic-ischemic insult is not neuroprotective. Pediatr Res 2001; 0(3): 405-11.**

**Abstract**

Three to 12 h of mild hypothermia (HT) starting after hypoxia-ischemia is neuroprotective in piglets that are anesthetized during HT. Newborn infants suffering from neonatal encephalopathy often ventilate spontaneously and are not necessarily sedated. We aimed to test whether mild posthypoxic HT lasting 24 h was neuroprotective if the animals were not sedated. Thirty-nine piglets (median weight 1.6 kg, range 0.8-2.2 kg; median age 24 h, range 7-48 h) were anesthetized and ventilated and subjected to a 45-min hypoxic (FiO<sub>2</sub> approximately 6%) global insult (n = 36) or sham hypoxia (n = 3). On reoxygenation, 18 were maintained normothermic (NT, 39.0 degrees C) for 72 h, and 21 were cooled from 39 (NT) to 35 degrees C (HT) for the first 24 h before NT was resumed (18 experimental, three sham hypoxia). Cardiovascular parameters and intermittent EEG were documented throughout. The brain was perfusion fixed for neuropathology and five main areas examined using light microscopy. The insult severity (duration in minutes of EEG amplitude < 7 microV) was similar in the NT and HT groups, mean +/- SD (28 +/- 7.2 versus 27 +/- 8.6 min), as was the mean FiO<sub>2</sub> (5.9 +/- 0.7 versus 5.8 +/- 0.8%) during the insult. Six NT and seven HT piglets developed posthypoxic seizures that lasted 29 and 30% of the time, respectively. The distribution and degree of injury (0.0-4.0, normal-maximal damage) within the brain (hippocampus, cortex/white matter, cerebellum, basal ganglia, thalamus) were similar in the NT and HT groups (overall score, mean +/- SD, 2.3 +/- 1.5 versus 2.4 +/- 1.3) as was the EEG background amplitude at 3 h (13 +/- 3.5 versus 10 +/- 3.3 microV). The HT animals shivered and were more active. The sham control group (n = 3) shivered but had normal physiology and neuropathology. Plasma cortisol was significantly higher in the HT group during the HT period, 766 +/- 277 versus 244 +/- 144 microM at 24 h. Mild postinsult HT for 24 h was not neuroprotective in unsedated piglets and did not reduce the number of animals that developed posthypoxic seizures. Cortisol reached 3 times the NT value at the end of HT. We speculate that the stress of shivering and feeling cold interfered with the previously shown neuroprotective effect of HT. Research on the appropriateness of sedation during clinical HT is urgent.

**Comments.** Study showing the important of timing

Level of Evidence: 6

Quality: Good

Evidence: Opposing

**Thoresen, M., M. Simmonds, et al. Effective selective head cooling during posthypoxic hypothermia in newborn piglets. Pediatr Res 2001; 49(4): 594-9. (LOE 6)**

**Abstract**

Selective head cooling has been proposed as a neuroprotective intervention after hypoxia-ischemia in which the brain is cooled without subjecting the rest of the body to significant hypothermia, thus minimizing adverse systemic effects. There are little data showing it is possible to cool the brain more than the body. We have therefore applied selective head cooling to our hypoxia-ischemia piglet model to establish whether it is possible. Nine piglets were anesthetized, and brain temperature was measured at the surface and in the superficial (0.2 cm) and deep (1.7-2.0 cm) gray matter. Rectal (6-cm depth), skin, and scalp temperatures (T) were recorded continuously. Lowering T-rectal from normothermia (39 degrees C) to hypothermia (33.5-33.8 degrees C) using a head cap perfused with cold (6-24 degrees C) water was undertaken for up to 6 h. To assess the impact of the 45-min hypoxia-ischemia insult on the effectiveness of selective head cooling, four piglets were cooled both before and after the insult, and four, only afterward. During selective head cooling, it was possible to achieve a lower T-deep brain than T-rectal in all animals both before and after

hypoxia. However, this was only possible when overhead body heating was used. The T-rectal to T-deep brain gradient was significantly smaller after the insult (median, 5.3 degrees C; range, 4.2-8.5 degrees C versus 3.0 degrees C; 1.7-7.4 degrees C;  $p = 0.008$ ). During rewarming to normothermia, the gradient was maintained at 4.5 degrees C. We report for the first time a study, which by direct measurement of deep intracerebral temperatures, validates the cooling cap as an effective method of selective brain cooling in a newborn animal hypoxia-ischemia model.

Level of Evidence: 6

Quality: Fair

Evidence: Supportive study

**Tooley, J. R., S. Satas, et al. Head cooling with mild systemic hypothermia in anesthetized piglets is neuroprotective. Ann Neurol 2003;53(1)**

**Abstract**

Hypothermia is potentially therapeutic in the management of neonatal hypoxic-ischemic brain injury. However, not all studies have shown a neuroprotective effect. It is suggested that the stress of unsedated hypothermia may interfere with neuroprotection. We propose that selective head cooling (SHC) combined with mild total-body hypothermia during anesthesia enhances local neuroprotection while minimizing the occurrence of systemic side effects and stress associated with unsedated whole-body cooling. Our objective was to determine whether SHC combined with mild total-body hypothermia while anesthetized for a period of 24 hours reduces cerebral damage in our piglet survival model of global hypoxia-ischemia. Eighteen anesthetized piglets received a 45-minute global hypoxic-ischemic insult. The pigs were randomized either to remain normothermic or to receive SHC. We found that the severity of the hypoxic-ischemic insult was similar in the SHC versus the normothermic group, and that the mean neurology scores at 30 and 48 hours and neuropathology scores were significantly better in the SHC group versus the normothermic group. We conclude that selective head cooling combined with mild systemic hypothermia and anesthesia is neuroprotective when started immediately after the insult in our piglet model of hypoxic-ischemic encephalopathy.

Level of Evidence: 6

Quality: Fair

Evidence: Supportive study

**Wagner, B. P., J. Nedelcu, et al. Delayed postischemic hypothermia improves long-term behavioral outcome after cerebral hypoxia-ischemia in neonatal rats. Pediatr Res 2002; 51(3): 354-60.(LOE 6)**

**Abstract**

Hypothermia may be an ideal neuroprotective intervention in hypoxic-ischemic encephalopathy after perinatal asphyxia. The present study describes the long-term effects of prolonged resuscitative whole-body hypothermia initiated 2 h after hypoxic-ischemic injury on brain morphology and neuropsychological behavior in 7-d-old rats. After right common carotid artery ligation and exposure to hypoxia of 8% O<sub>2</sub> for 105 min, 10 animals were kept normothermic at 37 degrees C and 10 animals were cooled to 30 degrees C rectal temperature for 26 h, starting 2 h after the hypoxic-ischemic insult. All hypoxic-ischemic animals were gavage fed to guarantee long-term survival. Neuroprotection was evaluated by magnetic resonance imaging and behavioral testing. Hypothermia significantly reduced the final size of cerebral infarction by 23% at 6 wk after the insult. The most extended tissue rescue was found in the hippocampus (21%,  $p = 0.031$ ), followed by the striatum (13%,  $p = 0.143$ ) and the cortex (11%,  $p = 0.160$ ). Cooling salvaged spatial memory deficits verified at 5 wk of recovery with Morris Water Maze test; whereas circling abnormalities after apomorphine injection and sensory motor dysfunctions on rotating treadmill improved, yet did not reach statistical significance. When compared with controls, hypoxic-ischemic animals performed worse in all behavioral tests. Hypothermia did not influence functional outcome in controls. Significant correlations between behavioral performance and corresponding regional brain volumes were found. We conclude that 26 h of mild to moderate resuscitative hypothermia leads not only to brain tissue rescue, but most important to long-lasting behavioral improvement throughout brain maturation despite severity of injury and delayed onset of cooling.

Level of Evidence: 6

Quality: Fair

Evidence: Supportive study

**Zhou, W. H., X. M. Shao, et al. Safety study of hypothermia for treatment of hypoxic-ischemic brain damage in term neonates. Acta Pharmacologica Sinica 2002; 23(SUPPL): 64-68.**

**Abstract**

**Objective** To investigate safety and efficacy of mild hypothermia by selective head cooling in term neonates with hypoxic-ischemic brain damage (HIBD). **METHODS:** Fifty term neonates with Apgar scores  $\leq 5$  at 5 min, and/or evidence of encephalopathy within 6 h after birth, were randomized to either noncooling, normothermia (NORM, n=27), or mild hypothermia group (HYPO, n=23), in which head cooling was induced by circulating water for 72 h. Neurodevelopment outcome was assessed at 6 month. **RESULTS:** The heart rates of the HYPO at 24, 48, and 72 h after treatment dropped to  $96 \pm 12$ ,  $85 \pm 9$ , and  $96 \pm 16$ , whereas that of the NORM to  $123 \pm 10$ ,  $125 \pm 13$  and  $121 \pm 19$ , respectively ( $P < 0.05$ ). There was no difference regarding ejection fraction (EF), stroke volume (SV) and cardiac output (CO) between the two groups ( $0.61 \pm 0.04$ ) vs ( $0.58 \pm 0.06$ ), ( $2.3 \pm 0.5$ ) vs ( $2.4 \pm 0.4$ ) mL/kg, ( $256 \pm 54$ ) vs ( $277 \pm 42$ ) mL [middle dot] kg<sup>-1</sup> [middle dot] min<sup>-1</sup>, respectively]. D-dimer and [beta]-tubulin were elevated in both groups. The neuron specific enolase (NSE) level of CSF was ( $26.2 \pm 10.8$ ) mg/L in the HYPO and ( $34.6 \pm 17.1$ ) mg/L in the NORM ( $P < 0.05$ ). Glutamic acid (GA) was lower in the HYPO [ $2.4 \pm 0.8$ ] vs [ $2.9 \pm 1.1$ ] mmol/L,  $P < 0.05$ ]. The neurodevelopment outcome of the patients at 6 mo showed that 18 of 23 patients in the HYPO (78.3 %) were considered to have a normal developmental quotient (DQ) compared with 19 of 27 (70.4 %) in the NORM. **CONCLUSION:** The results of our pilot study suggest that mild hypothermia does not aggravate cardiac, kidney and coagulation function, but has a potential of neuroprotection, It warrants a randomized controlled clinical study to verify its efficacy in HIBD.

**Comments** Randomized controlled study to address the question of hypothermia for neuroprotection. Numbers in this study too small to show an effect. Intervention was not associated with untoward side effects.

Level of Evidence: 2

Quality: Fair

Evidence: Supportive study

**Zhu, C., X. Wang, et al. Post-ischemic hypothermia-induced tissue protection and diminished apoptosis after neonatal cerebral hypoxia-ischemia. Brain Research 2004 996(1): 67-75. (LOE 6)**

**Abstract**

Hypothermia is possibly the single most effective method of neuroprotection developed to date. However, the mechanisms are not completely understood. The aim of this study was to investigate the effects of post-ischemic hypothermia on brain injury and apoptotic neuronal cell death as well as related biochemical changes after neonatal hypoxia-ischemia (HI). Seven-day-old rats were subjected to left common carotid artery ligation and hypoxia (7.8%) for 1 h. Systemic hypothermia was induced immediately after hypoxia-ischemia, and body temperature was maintained at 30 [degrees]C for 10 h. The normothermic group was kept at 36 [degrees]C. Brain infarct volumes and neuronal loss in the CA1 area of the hippocampus were significantly reduced at 72 h post-HI in the hypothermia group. Cytochrome c release and activation of caspase-3 and -2 at 24 h post-HI were significantly diminished by hypothermia. The numbers of cytochrome c- and TUNEL-positive cells in the cortex and dentate gyrus of the hippocampus were significantly reduced in the hypothermia group compared with the normothermia group at 72 h post-HI. These results indicate that hypothermia may, at least partially, act through inhibition of the intrinsic pathway of caspase activation in the neonatal brain, thereby preventing apoptotic cell death.

**Jacobs S, Hunt R, Tarnow-Mordi W, Inder T, Davis P Cooling for newborns with hypoxic ischaemic encephalopathy (Cochrane Review). In: The Cochrane Library, Issue 3, 2004. Chichester, UK: John Wiley & Sons, Ltd**

**Background:** Newborn animal and human pilot studies suggest that mild hypothermia following peripartum hypoxia-ischaemia in newborn infants may reduce neurological sequelae, without adverse effects.

**Objectives** To determine whether therapeutic hypothermia in encephalopathic asphyxiated newborn infants reduces mortality and long-term neurodevelopmental disability, without clinically important side effects.

**Methods** Randomised controlled trials evaluating therapeutic hypothermia in term newborns with hypoxic ischaemic encephalopathy were identified by searching the Oxford Database of Perinatal Trials, the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library Issue Issue 2, 2003), MEDLINE (1966 to July 2003), previous reviews including cross-references, abstracts, conferences, symposia proceedings, expert informants and journal hand searching. **Selection Criteria** Randomised controlled trials comparing the use of therapeutic hypothermia with normothermia in encephalopathic newborn infants with evidence of peripartum asphyxia and without recognisable major congenital anomalies were included. The primary outcome measure was death or long-term major neurodevelopmental disability. Other outcomes included adverse effects of cooling and 'early' indicators of neurodevelopmental outcome. **Data collection and analysis** Three reviewers independently selected, assessed the quality of and extracted data from the included studies. Authors were contacted for further information. Meta-analyses were performed using relative risk and risk difference for dichotomous data, and weighted mean difference

for continuous data with 95% confidence intervals. **Main Results** Two randomised controlled trials Gunn and Shankaran (described above) were included in this review, comprising 50 term infants with moderate/severe encephalopathy and evidence of intrapartum asphyxia. **Conclusions** There was no significant effect of therapeutic hypothermia on the combined outcome of death or major neurodevelopmental disability in survivors followed. No adverse effects of hypothermia on short term medical outcomes or on some 'early' indicators of neurodevelopmental outcome were detected. **Reviewers' conclusions**

Although two small randomised controlled trials demonstrated neither evidence of benefit or harm, current evidence is inadequate to assess either safety or efficacy of therapeutic hypothermia in newborn infants with hypoxic ischaemic encephalopathy. Therapeutic hypothermia for encephalopathic asphyxiated newborn infants should be further evaluated in well designed randomised controlled trials.

#### **Cochrane Review**

**Jacobs S, Hunt R, Tarnow-Mordi W, Inder T, Davis P** Cooling for newborns with hypoxic ischaemic encephalopathy (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2004. Chichester, UK: John Wiley & Sons, Ltd.

#### **Background**

Newborn animal and human pilot studies suggest that mild hypothermia following peripartum hypoxia-ischaemia in newborn infants may reduce neurological sequelae, without adverse effects. **Objectives** To determine whether therapeutic hypothermia in encephalopathic asphyxiated newborn infants reduces mortality and long-term neurodevelopmental disability, without clinically important side effects. **Search Strategy** The standard search strategy of the Neonatal Review Group as outlined in the Cochrane Library (Issue 2, 2003) was used. Randomised controlled trials evaluating therapeutic hypothermia in term newborns with hypoxic ischaemic encephalopathy were identified by searching the Oxford Database of

Perinatal Trials, the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library Issue Issue 2, 2003), MEDLINE (1966 to July 2003), previous reviews including cross-references, abstracts, conferences, symposia proceedings, expert informants and journal hand searching.

**Selection Criteria** Randomised controlled trials comparing the use of therapeutic hypothermia with normothermia in encephalopathic newborn infants with evidence of peripartum asphyxia and without recognisable major congenital anomalies were included. The primary outcome measure was death or long-term major neurodevelopmental disability. Other outcomes included adverse effects of cooling and 'early' indicators of neurodevelopmental outcome. **Results** Two randomised controlled trials (**Gunn and Shankaran- both reviewed above**) were included in this review, comprising 50 term infants with moderate/ severe encephalopathy and evidence of intrapartum asphyxia. There was no significant effect of therapeutic hypothermia on the combined outcome of death or major neurodevelopmental disability in survivors followed. No adverse effects of hypothermia on short term medical outcomes or on some 'early' indicators of neurodevelopmental outcome were detected.

**Reviewers' conclusions** Although two small randomised controlled trials demonstrated neither evidence of benefit or harm, current evidence is inadequate to assess either safety or efficacy of therapeutic hypothermia in newborn infants with hypoxic ischaemic encephalopathy. Therapeutic hypothermia for encephalopathic asphyxiated newborn infants should be further evaluated in well designed randomised controlled trials.

**Critique** The review offers less than this worksheet. It has not included a couple of randomized studies.