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

Worksheet author(s) | Date Submitted for review: 4/21/08 revised 10/8/09

Clinical question.
In term infants at risk for hypoxic-ischemic encephalopathy secondary to intra-partum hypoxia does selective/whole body cooling as opposed to standard care (without cooling) improve outcome?

Is this question addressing an intervention/therapy, prognosis or diagnosis? Intervention
State if this is a proposed new topic or revision of existing worksheet: Revision of an existing worksheet

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

Search strategy (including electronic databases searched).
Mesh terms included hypothermia, induced hypothermia, body cooling, whole body cooling, selective head cooling, neonate, asphyxia, hypoxia ischemia, hypoxia, body temperature, animal, seizures brain diseases
Medline: (1966-2009) Hypothermia + Hypoxia-ischemia – 69 hits of which 35 were reviewed, Hypoxia-Ischemia + Newborn +hypothermia- 20 hits-19 were reviewed, Asphyxia + hypothermia-7 hits- all reviewed, Induced hypothermia+ newborn-13 hits-all reviewed, whole body cooling –94 hits-10 reviewed, seizures +hypothermia+ newborn- 10 hits-4 reviewed
Embase: Asphyxia+ hypothermia- 134 hits-27 reviewed, asphyxia+ body temperature- 27 hits-6 reviewed, asphyxia+newborn+hypothermia-58 hits-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. Endnote library- 68 hits
There is one relevant new Cochrane review Cooling for newborns with hypoxic ischaemic encephalopathy. [update of Cochrane Database Syst Rev. 2007; (4):CD003311; PMID: 14583966]

• State inclusion and exclusion criteria
  For this worksheet I included all the neonatal human studies that have been published since the last review and excluded any animal studies performed since the last worksheet completed in February 2005. The most recent search was through October 2009

• Number of articles/sources meeting criteria for further review:
  The previous worksheet contained 29 articles. Since that time there has been two large randomized studies, two small randomized studies, one of which was termed a pilot study that has both a safety and efficacy arm, an updated Cochrane review; all will be included in the worksheet grid. There have been 9 review articles on the subjects and several manuscripts using data from one of the randomized studies that were also reviewed but not included in the worksheet but will be available as a source of reference.
## Summary of evidence

### Evidence Supporting Clinical Question

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**Level of evidence**

A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = Other endpoint  
*Italics = Animal studies*
### Evidence Neutral to Clinical question

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**Level of evidence**

| 1 | 2 | 3 | 4 | 5 |

A = Return of spontaneous circulation  
B = Survival of event  
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### Evidence Opposing Clinical Question

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| Fair |  |  |  |  | **Gunn, 1998 E**  
**Gunn, 1999 E**  
**Laptook, 1999 E**  
**Thoresen, 2001 E** |
| Poor |  |  |  |  |  |

**Level of evidence**

| 1 | 2 | 3 | 4 | 5 |

A = Return of spontaneous circulation  
B = Survival of event  
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*Italics = Animal studies*
REVIEWER'S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

Modest systemic or selective cooling of the brain by as little as 2°C-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) and more recently in newborns. Three large randomized studies (Gluckman, 2005 #31 (selective head cooling), Shankaran, 2005 #32 (whole body cooling)), one randomized pilot study (Eicher, 2005 #34) (whole body cooling) and one quasi randomized study (Lin, 2006 #30).

Three large randomized multicenter studies i.e. Cool Cap study (Gluckman, 2005 #31) whole body cooling (Shankaran, 2005 #32), and Azzopardi # (TOBY) included infants with a gestational age ≥36 weeks treated at or before six hours of age with either severe acidosis or perinatal complications and resuscitation at birth and who had moderate or severe encephalopathy. In the Cool Cap and TOBY studies enrollment included an aEEG determination of moderate/severe encephalopathy + clinical whereas the whole body cooling utilized clinical criteria of moderate/severe encephalopathy (Sarnat classification). The Cool Cap study cooled to a rectal temperature of 34.5°C and whole-body cooling and TOBY studies to an esophageal or rectal temperature of 33.5°C; for 72 hours, followed by slow rewarming (hypothermia group). Neurodevelopmental outcome was assessed at 18 to 22 months of age with a primary outcome of a combined end point of death or severe disability (Cool Cap, TOBY) or death or moderate or severe disability (whole body cooling). The Cool-cap study failed to show an overall significant effect of cooling in reducing death and or severe neurodevelopmental deficits (OR0.61 (95%CI 0.43-1.09), however for infants with moderate encephalopathy there was a significant effect OR0.61 (95%CI 0.43-1.09) whereas with severe encephalopathy and/or seizures no effect was noted (p=0.51). In the whole body study, a significant reduction in death and moderate/severe encephalopathy was noted (RR 0.72 (95%CI 0.54-.095) whereas there was no significant effect when these items were analyzed individually i.e. death (RR 0.68 (95%CI 0.44-.105), moderate encephalopathy (RR 0.68 (95%CI 0.44-.107) and severe encephalopathy (RR 0.85 (95%CI 0.64-.113). In the latter study the number needed to treat to show benefit in one infant was six. In the TOBY study in the cooled group, 42 infants died and 32 survived but had severe neurodevelopmental disability, whereas in the noncooled group, 44 infants died and 42 had severe disability (relative risk for either outcome, 0.86; 95% confidence interval [CI], 0.68 to 1.07; P=0.17). Infants in the cooled group had an increased rate of survival without neurologic abnormality (relative risk, 1.57; 95% CI, 1.16 to 2.12; P=0.003). Among survivors, cooling resulted in reduced risks of cerebral palsy (relative risk, 0.67; 95% CI, 0.47 to 0.96; P=0.03) and improved scores on the Mental Developmental Index and Psychomotor Developmental Index of the Bayley Scales of Infant Development II (P=0.03 for each) and the Gross Motor Function Classification System (P=0.01). In the pilot study of (Eicher, 2005 #34) whole body cooling was maintained at 33.5°C for 48 hours. At one year outcome, no different in cognitive scores were noted, however death and severe outcome was significantly less in infants who were cooled compared to comparison group (p=0.01). Importantly approximately 20 per cent in each group were lost to follow-up. In the study of (Lin, 2006 #30) a quasi randomized approach was used (alternate day) and whole body cooling to a temperature of 34 to 35°C was implemented. At seven day follow-up the CT scan showed significantly less severe disease and there was improved neurobehavioral scores in the hypothermic group. When the outcome data for the major studies are pooled and analyzed as a function of the severity of encephalopathy, the only significant effects were noted in those infants who presented with moderate encephalopathy as it related to death and moderate/severe encephalopathy (RR 0.72 (95%CI 0.58-.91) and severe cerebral palsy (RR 0.42 (95% CI 0.19-.92) (Shah, 2007 #4). Some adverse effects of hypothermia included an increase in the need for inotrope support and a significant increase in thrombocytopenia. (Jacobs, 2007 #35)

**Conclusion**

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

**CONSENSUS ON SCIENCE:**

Evidence from three good randomized studies (LOE1 Gluckman 2005; 663, Shankaran 2005; 1574, Azzopardi 2009, 1341) and two small fair randomized trials (LOE 1, Eicher 2005; 11, Lin 2006; 180) demonstrate that induced hypothermia implemented within six hours of age in infants at highest risk for brain injury is associated with significantly less death and neurodevelopmental disability at 18 month follow-up and particularly in those infants who present with moderate encephalopathy. Hypothermia is associated with an increase use of inotropes as well as with thrombocytopenia.

**TREATMENT RECOMMENDATION:**

**Acknowledgements:**
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*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.*
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: 1
Quality: Fair
Evidence: Supportive


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)) x 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: 4
Quality: Fair
Evidence: Supportive

ABSTRACT
Background Whether hypothermic therapy improves neurodevelopmental outcomes in newborn infants with asphyxial encephalopathy is uncertain. Methods We performed a randomized trial of infants who were less than 6 hours of age and had a gestational age of at least 36 weeks and perinatal asphyxial encephalopathy. We compared intensive care plus cooling of the body to 33.5°C for 72 hours and intensive care alone. The primary outcome was death or severe disability at 18 months of age. Prespecified secondary outcomes included 12 neurologic outcomes and 14 other adverse outcomes.

Results Of 325 infants enrolled, 163 underwent intensive care with cooling, and 162 underwent intensive care alone. In the cooled group, 42 infants died and 32 survived but had severe neurodevelopmental disability, whereas in the noncooled group, 44 infants died and 42 had severe disability (relative risk for either outcome, 0.86; 95% confidence interval [CI], 0.68 to 1.07; P=0.17). Infants in the cooled group had an increased rate of survival without neurologic abnormality (relative risk, 1.57; 95% CI, 1.16 to 2.12; P=0.003). Among survivors, cooling resulted in reduced risks of cerebral palsy (relative risk, 0.67; 95% CI, 0.47 to 0.96; P=0.03) and improved scores on the Mental Developmental Index and Psychomotor Developmental Index of the Bayley Scales of Infant Development II (P=0.03 for each) and the Gross Motor Function Classification System (P=0.01). Improvements in other neurologic outcomes in the cooled group were not significant. Adverse events were mostly minor and not associated with cooling.

Conclusions Induction of moderate hypothermia for 72 hours in infants who had perinatal asphyxia did not significantly reduce the combined rate of death or severe disability but resulted in improved neurologic outcomes in survivors.

Comment Randomized study with findings consistent with the two prior studies. Although the composite outcome i.e. death/severe disability was not different, secondary outcomes survival without neurologic disability and cerebral palsy was improved with cooling

Level of Evidence: 1
Quality: Good
Evidence: Positive treatment effect in the treated group of survivors


Abstract
OBJECTIVES: To determine the neurodevelopmental outcome of infants treated with head cooling with systemic hypothermia after hypoxic-ischemic encephalopathy. STUDY DESIGN: Infants >/=37 weeks' gestation, who had an umbilical artery pH </=7.09 or Apgar score </=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 +/- 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 +/- 0.5 degrees C (n = 6) or 34.5 +/- 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: 2
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 10⁹/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: 2
Quality: Fair
Evidence: Supportive


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 (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: 5
Quality: Good
Evidence: Supportive


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 +/- 35 versus 100 +/- 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: 5
Quality: Good
Evidence: Supportive

**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 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

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**Background:** Several studies have demonstrated the efficiency and safety of mild hypothermia (33°C) used for treating moderate encephalopathy. In animal models, deep hypothermia proved to be neuroprotective. **Objectives:** To determine the safety of whole-body deep hypothermia between 30 and 33°C in moderate-severe hypoxic-ischemic encephalopathy in newborn term infants. **Methods:** Mortality rates, incidence of brain damage detected by magnetic resonance imaging (MRI) and neurological outcomes of 39 term asphyxiated infants were retrospectively compared. A first group of patients (control group C) was treated with routine standard methods, a second group (MH) was treated with mild whole-body hypothermia (32-34°C) and a third group (DH) was treated with deep whole-body hypothermia (30-33°C), for 72 h. Mean arterial pH, basic excess (BE) and lactic acid in the blood were measured. Laboratory and clinical side effects of hypothermia were investigated. A conventional brain MRI was performed after the second week of life. **Results:** 39 term asphyxiated newborns were enrolled in the study: 11 in group C, 10 in group MH, and 18 in group DH. During the first 72 h, disseminated intravascular coagulation was recorded in 2 cases (18%) in group C, pulmonary hypertension in 2 patients (20%) in group MH, and pneumonia in 3 cases (16%) in group DH. Severe cerebral lesions and poor neurological outcome were observed in 4 cases (36%) in group C, 1 case (10%) in group MH, and 1 case (5%) in group DH. A statistically significant difference in brain damage and major clinical neurological abnormalities was observed between group C and groups MH and DH, whereas no differences were demonstrated between asphyxiated infants treated with mild or deep hypothermia. **Conclusions:** The results support the safety of deep hypothermia. Further studies are needed to confirm these results and the neuroprotective effect of this approach.

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**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

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Hypoxic-ischemic injury may cause multisystem organ damage with significant aberrations in clotting, renal, and cardiac functions. Systemic hypothermia may aggravate these medical conditions, such as bradycardia and increased clotting times, and very little safety data in neonatal hypoxic-ischemic injury is available. This study reports a multicenter, randomized, controlled pilot trial of moderate systemic hypothermia (33 degrees C) vs normothermia (37 degrees C) for 48 hours in infants with neonatal encephalopathy instituted within 6 hours of birth or hypoxic-ischemic event. The best outcome measures of safety were determined, comparing rates of adverse events between normothermia and hypothermia groups. A total of 32 hypothermia and 33 normothermia neonates were enrolled in seven centers. The following adverse events were observed significantly more commonly in the hypothermia group: more frequent bradycardia and lower heart rates during the period of hypothermia, longer
dependence on pressors, higher prothrombin times, and lower platelet counts with more patients requiring plasma and platelet transfusions. Seizures as an adverse event were more common in the hypothermia group. These observed side effects of 48 hours of moderate systemic hypothermia were of mild to moderate severity and manageable with minor interventions.

Comments Pilot study showing a longer dependent on pressors, higher PTT,PT, lowere platelets andmore requiring FFP and platelets

Level of Evidence: 1
Quality: Fair
Evidence: Increased side effects in the hypothermia group


Cerebral hypothermia can improve outcome of experimental perinatal hypoxia-ischaemia. A multicentre randomized controlled trial was undertaken to determine whether delayed head cooling can improve neurodevelopmental outcome in babies with neonatal encephalopathy.

METHODS: 234 term infants with moderate to severe neonatal encephalopathy and abnormal amplitude integrated electroencephalography (aEEG) were randomly assigned to either head cooling for 72 h, within 6 h of birth, with rectal temperature maintained at 34-35 degrees C (n=116), or conventional care (n=118). Primary outcome was death or severe disability at 18 months. Analysis was by intention to treat. We examined in two predefined subgroup analyses the effect of hypothermia in babies with the most severe aEEG changes before randomisation--ie, severe loss of background amplitude, and seizures--and those with less severe changes. Results In 16 babies, follow-up data were not available. Thus in 218 infants (93%), 73/110 (66%) allocated conventional care and 59/108 (55%) assigned head cooling died or had severe disability at 18 months (odds ratio 0.61; 95% CI 0.34-1.09, p=0.05). No difference was noted in the frequency of clinically important complications. Predefined subgroup analysis suggested that head cooling had no effect in infants with the most severe aEEG changes (n=46, 1.8; 0.49-6.4, p=0.51), but was beneficial in infants with less severe aEEG changes (n=172, 0.42; 0.22-0.80, p=0.009). Results: These data suggest that although induced head cooling is not protective in a mixed population of infants with neonatal encephalopathy, it could safely improve survival without severe neurodevelopmental disability in infants with less severe aEEG changes.

Comments Large multicenter study that did not show an overall treatment effect but in infants with moderate encephalopathy and no seizures at enrollment there was a significant effect

Level of Evidence: 1
Quality: Good
Evidence: Positive treatment effect in a subcategory of patients


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: 5
Quality: Excellent
Evidence: Supportive


Abstract

Objective: Cerebral hypothermia has been shown to reduce damage from experimental hypoxia-ischemia 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 partial reticuloencephalographic 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
Level of Evidence: 5
Quality: Good
Evidence: Supportive


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 postsutlis, 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: 5
Quality: Good
Evidence: Negative study


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 unbilical 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 mild 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 to 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


**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 (FiO2) to the maximum concentration (approximately 6%) giving low amplitude (< 7.0 microV) EEG. FiO2 was temporarily increased if heart rate, blood pressure, or end expiratory partial pressure of alveolar CO2 (PaCO2) 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:** 5
**Quality:** Fair-
**Evidence:** Supportive study


**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 rewarthing. 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:** 4
**Quality:** Fair-
**Evidence:** Supportive study


**BACKGROUND:** Newborn animal studies and pilot studies in humans suggest that mild hypothermia following peripartum hypoxia-ischaemia in newborn infants may reduce neurological sequelae without adverse effects. OBJECTIVES: To determine the effect of therapeutic hypothermia in encephalopathic asphyxiated newborn infants on mortality, long-term neurodevelopmental disability and clinically important side effects. SEARCH STRATEGY: The standard search strategy of the Neonatal Review Group as outlined in The Cochrane Library (Issue 2, 2007) 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 2, 2007), MEDLINE (1966 to June 2007), 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 standard care in encephalopathic newborn infants with evidence of peripartum asphyxia and without recognizable 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 ANALYSIS: Three review authors 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: Eight randomised controlled trials were included in this review, comprising 638 term infants with moderate/severe encephalopathy and...
evidence of intrapartum asphyxia. Therapeutic hypothermia resulted in a statistically significant and clinically important reduction in the combined outcome of mortality or major neurodevelopmental disability to 18 months of age [typical RR 0.76 (95% CI 0.65, 0.89), typical RD -0.15 (95% CI -0.24, -0.07), NNT 7 (95% CI 4, 14)]. Cooling also resulted in statistically significant reductions in mortality [typical RR 0.74 (95% CI 0.58, 0.94), typical RD -0.09 (95% CI -0.16, -0.02), NNT 11 (95% CI 6, 50)] and in neurodevelopmental disability in survivors [typical RR 0.68 (95% CI 0.51, 0.92), typical RD -0.13 (95% CI -0.23, -0.03), NNT 8 (95% CI 4, 33)]. Some adverse effects of hypothermia included an increase in the need for inotrope support of borderline significance and a significant increase in thrombocytopenia.

CONCLUSIONS: There is evidence from the eight randomised controlled trials included in this systematic review (n = 638) that therapeutic hypothermia is beneficial to term newborns with hypoxic ischaemic encephalopathy. Cooling reduces mortality without increasing major disability in survivors. The benefits of cooling on survival and neurodevelopment outweigh the short-term adverse effects. However, this review comprises an analysis based on less than half of all infants currently known to be randomized into eligible trials of cooling. Incorporation of data from ongoing and completed randomised trials (n = 829) will be important to clarify the effectiveness of cooling and to provide more information on the safety of therapeutic hypothermia, but could also alter these conclusions. Further trials to determine the appropriate method of providing therapeutic hypothermia, including comparison of whole body with selective head cooling with mild systemic hypothermia, are required.

Comments Overall a good review however included small pilot studies in the overall review. Did not address the issue of different temperature used in the two major studies and the two different modes of cooling and its impact when performing a meta-analysis
Level of Evidence: 1
Quality: Good
Evidence: Supportive study


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


Abstract
Intraschismic 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 +/- .02 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: 5
Quality: Good
Evidence: Supportive review


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 intraischemic 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: 5
Quality: Good
Evidence: Negative

Lin ZL, Yu HM et al Mild hypothermia via selective head cooling as neuroprotective therapy in term neonates with perinatal asphyxia: an experience from a single neonatal intensive care unit
OBJECTIVE: The objective of this study was to determine the efficacy of mild hypothermia via selective head cooling as a neuroprotective therapy in term infants with perinatal asphyxia. STUDY DESIGN: Full-term newborns who had 5 min Apgar scores <6, first arterial blood gas pH<7.10 or BD>15 mEq/l, and with the clinical signs of encephalopathy were enrolled within 6 h after birth. Patients were randomized to receive mild hypothermia treatment via selective head cooling for a total of 72 h or receive routine treatment as a control. Brain hypoxic-ischemic injury was quantified based on the head computed tomographic scan (CT scan) at postnatal age 5-7 days and a Neonatal Behavioral Neurological Assessment (NBNA) score at 7-10 days of life. RESULTS: A total of 58 patients (30 hypothermia, 28 control) completed the study. Hypothermia was well tolerated in this study and attenuated the hypoxic-ischemic brain injury due to perinatal asphyxia. Head CT scan demonstrated moderate to severe hypoxic-ischemic changes in only 4/30 cases from the hypothermic group. In contrast, 18/28 cases in the control group showed moderate to severe hypoxic-ischemic changes (chi (2)=15.97, P<0.01). Brain hypothermia also significantly improved the NBNA score (32 +/- 2 in the hypothermic group vs 28 +/- 3 in the control group, P<0.01). CONCLUSIONS: Our results suggest that selective head cooling may be used as a neuroprotective therapy in term neonates with perinatal asphyxia. A long-term follow-up study is needed to further validate the results of this study.

Level of Evidence: 1
Quality: Good
Evidence: Negative


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: 5
Quality: Fair
Evidence: Supportive study

**Shankaran S, Laptokar AR et al Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy**

BACKGROUND: Hypothermia is protective against brain injury after asphyxia in animal models. However, the safety and effectiveness of hypothermia in term infants with encephalopathy is uncertain. METHODS: A randomized trial of hypothermia was conducted in infants with a gestational age of at least 36 weeks who were admitted to the hospital at or before six hours of age with either severe acidosis or perinatal complications and resuscitation at birth and who had moderate or severe encephalopathy. Infants were randomly assigned to usual care (control group) or whole-body cooling to an esophageal temperature of 33.5 degrees C for 72 hours, followed by slow rewarming (hypothermia group). Neurodevelopmental outcome was assessed at 18 to 22 months of age. The primary outcome was a combined end point of death or moderate or severe disability. RESULTS: Of 239 eligible infants, 102 were assigned to the hypothermia group and 106 to the control group. Adverse events were similar in the two groups during the 72 hours of cooling. Primary outcome data were available for 205 infants. Death or moderate or severe disability occurred in 45 of 102 infants (44 percent) in the hypothermia group and 64 of 103 infants (62 percent) in the control group (risk ratio, 0.72; 95 percent confidence interval, 0.54 to 0.95; P=0.01). Twenty-four infants (24 percent) in the hypothermia group and 38 (37 percent) in the control group died (risk ratio, 0.68; 95 percent confidence interval, 0.44 to 1.05; P=0.08). There was no increase in major disability among survivors; the rate of cerebral palsy was 15 of 77 (19 percent) in the hypothermia group as compared with 19 of 64 (30 percent) in the control group (risk ratio, 0.68; 95 percent confidence interval, 0.38 to 1.22; P=0.20). CONCLUSIONS: Whole-body hypothermia reduces the risk of death or disability in infants with moderate or severe hypoxic-ischemic encephalopathy.

Comments Large multicenter study that shows a beneficial effect of whole body cooling in reducing death and/or moderate/severe neurodevelopmental deficits at 18 month followup. However when these items were evaluated individually, there were no significant differences

Level of Evidence:1
Quality: Good
Evidence: Supportive study


Objectives To systematically review the effectiveness, as determined by survival without moderate to severe neurodevelopmental disability in infancy and childhood, and the safety of hypothermia vs normothermia in neonates with postintrapartum hypoxic-ischemic encephalopathy and to perform subgroup analyses based on severity of encephalopathy (moderate or severe), type of hypothermia (systemic or selective head cooling), and degree of hypothermia (moderate ([&le;]32.0-33.5[degrees]C) or mild ([&ge;]33.6[degrees]C]). Data Sources MEDLINE, EMBASE, CINAHL (Cumulative Index for Nursing and Allied Health Literature), the Cochrane Library, abstracts of annual meetings of the Pediatric Academic Societies, and bibliographies of identified articles. Study Selection Randomized and quasi-randomized controlled trials without language restriction were assessed by 2 reviewers independently and discrepancies were resolved by involving a third reviewer. Quality of the trials was assessed on the basis of concealment of allocation, method of randomization, masking of outcome assessment, and completeness of follow-up. Intervention Systemic or selective head hypothermia compared with normothermia. Main Outcome Measure Death or moderate to severe neurodevelopmental disability. Results Eight studies of acceptable quality were included. The combined outcome of death or neurodevelopmental disability in childhood was reduced in infants receiving hypothermia compared with control infants (4 studies including 497 infants; relative risk, 0.76; 95% confidence interval, 0.65-0.88; number needed to treat, 6; 95% confidence interval, 4-14), as were death and moderate to severe neurodevelopmental disability when analyzed separately. Cardiac arrhythmias and thrombocytopenia were more common with hypothermia; however, they were clinically benign. Conclusions In neonates with postintrapartum asphyxial hypoxic-ischemic encephalopathy, hypothermia is effective in reducing death and moderate to severe neurodevelopmental disability either in combination or separately and is a safe intervention.

Level of Evidence: 1
Quality: Good
Evidence: Supportive analysis


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 neurologic 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 neurologic 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


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(2) 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 phosphorous 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, cerebral energy metabolism was measured by phosphorous 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: 5
Quality: Fair
Evidence: Supportive study


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 to 34 degrees C). Results Seventy-five of the 148 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
Hypothermia is potentially therapeutic in the management of neonatal hypoxic-ischemic brain injury. However, not all studies have shown a beneficial effect. Eighteen anesthetized piglets received a 45-minute global hypoxic-ischemic insult. The pigs were randomized either to remain normothermic or to receive 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. 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; 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: 5
Quality: Good
Evidence: Opposing


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(2) 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(2) (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: 5
Quality: Good
Evidence: Opposing


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: 5
Quality: Fair
Evidence: Supportive study


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.
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(2) 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.


**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 <=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+/-12, 85+/-9, and 96+/-16, whereas that of the NORM to 123+/-10, 125+/-13 and 121+/-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+/-0.04) vs (0.58+/-0.06), (2.3+/-0.5) vs (2.4+/-0.4) mL/kg, (256+/-54) vs (277+/-42) mL/min/kg, respectively. D-dimmer and [beta]MG were elevated in both groups. The neuron specific enolase (NSE) level of CSF was (26.2+/-10.8) mg/L in the HYPO and (34.6+/-17.1) mg/L in the NORM (P<0.05). Glutamic acid (GA) was lower in the HYPO [(2.4+/-0.8) vs (2.9+/-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 neurodevelopmental 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.


**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.
Level of Evidence: 5
Quality: Fair
Evidence: Supportive study