Hypothermia to Treat Neonatal Hypoxic Ischemic Encephalopathy

Systematic Review

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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 [$\leq 32.0\text{ - }33.5^\circ\text{C}$] or mild [$\geq 33.6^\circ\text{C}$]).

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.

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A systematic review of hypothermia (2 studies reported in 4 publications\textsuperscript{11-14}) used to treat neonatal HIE found a lack of evidence to support this intervention.\textsuperscript{15} Since then, several randomized controlled trials (RCTs) have been performed. Higgins\textsuperscript{16} reviewed only 2 large multicenter trials and identified deficiencies in our knowledge of this intervention. Speer and Perlman\textsuperscript{17} reviewed experimental studies, pilot (feasibility and safety) studies, and multicenter studies. Their review included both randomized and nonrandomized studies and excluded non–English literature studies, and several studies, including RCTs, were not assessed for safety. No meta-analytic techniques were used to describe either safety or efficacy.
Our primary objectives were to assess the effectiveness, as determined by survival without moderate to severe disability in infancy and childhood, and the safety of hypothermia vs normothermia in neonates with postintrapartum asphyxia due to HIE. Secondary objectives were 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 [≤32.0-33.5°C] or mild [≥33.6°C]).

METHODS

DATA SOURCES

MEDLINE (January 1, 1966, to December 31, 2006), EMBASE (January 1, 1980, to December 31, 2006), CINAHL (Cumulative Index to Nursing and Allied Health Literature; January 1, 1982, to December 31, 2006), the Cochrane Library (2006, issue 4), abstracts of the annual meetings of the Pediatric Academic Societies and the European Society of Pediatric Research (2001-2006), and bibliographies of identified articles were searched (December 2006). No language restrictions were applied. MeSH terms and text words for search used included the following: infant-newborn; infant, newborn; diseases; newborn infant; neonate (population); hypothermia; hypothermias; hypothermia, induced; cerebral hypothermia; circulatory arrest; deep hypothermia, induced; cooling; head cooling; whole body cooling (intervention); clinical trials; controlled clinical trials; randomized controlled trials; random allocation; multicenter studies; control groups; and evaluation studies (comparison). These were adjusted according to database-specific terms.

STUDY SELECTION

Randomized and quasi-randomized (eg, randomization on the basis of day, date, and hospital number) controlled trials of hypothermia (systemic or selective head cooling) were included. Retrospective studies, before-and-after comparisons, case series, case reports, letters to the editor not containing primary data, editorials, review articles, and commentaries were excluded but were read to identify potential studies. Duplicate reports not providing additional information were excluded. Randomized controlled trials in which neonates had clinical (including, but not limited to, low Apgar score, need for resuscitation, neurologic examination demonstrating evidence of encephalopathy with or without preceding intrapartum history indicative of the possibility of asphyxia), biochemical (umbilical arterial or immediate postnatal blood gas analyses revealing pH or acid-base deficit below a set cut-off point as defined in the study), and electrophysiologic evidence of HIE (amplitude-integrated electroencephalogram showing patterns indicative of moderate or severe encephalopathy) were included. Patients in the intervention arm must have received hypothermia (systemic or selective head cooling) for at least 24 hours.

DATA EXTRACTION

Identified studies were reviewed and data from eligible studies were abstracted independently by 2 of us (P.S.S. and A.O.) and compared. Discrepancies were resolved by consensus and involvement of a third author (M.P.). Methodological quality was assessed using the information in the original publications. Quality was assessed for allocation concealment (yes, no, or cannot tell), method of randomization (randomized or quasi-randomized), and masking of outcome assessment (yes, no, or cannot tell). The intervention could not be masked. A typical effect size was calculated and reported as relative risk (RR), risk difference, and number-needed-to-treat, as appropriate, with 95% confidence interval (CI). All analyses (fixed-effects model) were performed using Revman 4.3.8 software (Cochrane Collaboration, Oxford, England, and the University of Maryland Center for Integrative Medicine, Baltimore). The χ² test was applied to detect between-study heterogeneity, and the I² statistic was applied to assess the appropriateness of combining study results. No statistical corrections were used to adjust for multiple analyses. Publication bias was assessed by checking funnel plots.

OUTCOMES OF INTEREST

The primary outcome was survival without moderate to severe neurodevelopmental disability in infancy and childhood. Secondary outcomes assessed included (1) effectiveness outcomes including neurodevelopmental disability among survivors, severe visual deficit, severe hearing deficit, epilepsy, and cognitive or psychomotor delay, and (2) safety outcomes including death and cardiovascular (arrhythmia and hypertension), hematologic (platelet count <100, and clinical and laboratory evidence of altered coagulation), neurologic (seizures after enrollment), infectious (sepsis), renal (oliguria, defined as urine output <1 mL/kg/h; renal failure, defined as oliguria or anuria with rising creatinine level), hepatic (elevated liver enzyme levels), and electrolyte (hypoglycemia, defined as serum glucose concentration <47 mg/dL [to convert to millimoles per liter, multiply by 0.0555]; or hypokalemia, defined as serum potassium concentration <3.5 mEq/L [to convert to millimoles per liter, multiply by 1.01]) disorders. Severe neurodevelopmental disability was considered when cerebral palsy (nonambulatory, severe spasticity, or Gross Motor Functional Classification System class 3 or higher), Mental Developmental Index or Psychomotor Developmental Index of less than 70 for age, hearing deficit requiring hearing aids, or visual acuity less than 6/60 (Snellen 20/200) in either eye was present. Moderate neurodevelopmental disability was considered when moderate motor dysfunction (ambulatory cerebral palsy, moderate spasticity, or Gross Motor Functional Classification System class 2), Mental Developmental Index or Psychomotor Developmental Index 70 to 84 for age, or moderate hearing or visual deficit was present.

DATA ANALYSES

Inasmuch as this therapy is in the evaluation phase, we included data on efficacy from studies that reported childhood (age ≥12 months) outcomes only and data on safety from all studies that reported safety outcomes including death. Subgroup analyses were planned a priori on the basis of comparisons between patients with moderate or severe HIE (Sarnat and Sarnat20 or similar staging system or amplitude-integrated electroencephalographic findings suggestive of moderate to severe involvement21).

Sixteen studies were assessed for eligibility. Three retrospective studies, 22-24 3 case series,23,26 1 interim report of an ongoing RCT,27 and 1 study that reported only echocardiographic findings28 were excluded (Figure 1 ). Battin et al11,12 and Gunn et al13 published their results in 3 different reports. The last report11 comprised 9 nonrandomized infants, 7 who received hypothermia and 2 control infants. Data for the nonrandomized infants could not be separated out; thus, we only analyzed data pub-
lished in 1 of the reports that randomized patients to hypothermia or normothermia. For efficacy evaluation, 4 studies provided data on infancy or childhood outcomes, and for safety evaluation, data from all 8 studies were included. Of the 650 patients in these studies, only 19 patients with mild HIE were included in 4 studies. Two patients in the study by Eicher et al had postnatal asphyxia; 1 died and the data for the other infant were not reported separately. Four studies used systemic hypothermia and moderate hypothermia (≥33.6°C) in 4 studies and moderate hypothermia (≥33.6°C) in 4 studies. Systemic hypothermia was achieved using a plastic bag containing water and a cooling blanket in 1 study and precooled blankets in 1 study. The method of cooling was not reported in 1 study. Head cooling (which causes systemic hypothermia as well as head cooling) was achieved using a cap containing circulating cold water. The intervention period was 72 hours in 7 studies and 48 hours in 1 study. Infants were gradually rewarmed at 0.5°C per hour or allowed to warm passively in nursery temperature. No adverse effects were observed during re-warming.

Overall methodological quality of the studies was acceptable. Concealed allocation was performed in 6 studies, not reported in 1 study, and not done in 1 study. Seven studies were randomized trials and 1 was quasi-randomized; randomization was based on the day of admission. In all studies, the intervention was un-masked. Assessment of survivors at follow-up during childhood was reported in 4 studies, with 32% patients lost to follow-up in 1 study. Funnel plot assessment revealed a lack of studies at the extremes of point estimates and clustering of the studies at the point estimate, indicating minor heterogeneity in reported outcomes.

**PRIMARY OUTCOME**

There was a significant reduction in the risk of death or of moderate to severe neurodevelopmental disability (Figure 2) in infants who received hypothermia compared with control infants (RR, 0.76 [95% CI, 0.65-0.88]; risk difference, −0.16 [95% CI, −0.24 to 0.07]; number needed to treat, 6 [95% CI, 4-14]; test of heterogeneity, \(P = .54\) and \(I^2 = 0\)).

**EFFECTIVENESS OUTCOMES**

Compared with the control group, the hypothermia group showed a significant reduction in severe neurodevelopmental disability rate, severe cerebral palsy, and number of infants with a Mental Developmental Index or a Psychomotor Developmental Index less than 70 (Table 2). More infants in the control group died after withdrawal of life support.

**SAFETY OUTCOMES**

Mortality was reduced in the hypothermia group (RR, 0.74 [95% CI, 0.58-0.94]; risk difference, −0.09 [95% CI, −0.15 to 0.02]; number needed to treat, 11 [95% CI, 7-50]; test of heterogeneity, \(P = .91\) and \(I^2 = 0\)) (Table 2). Most studies reported associations between hypothermia (systemic and head cooling) and bradycardia. The rates of arrhythmia and thrombocytopenia were higher in the hypothermia group. Eicher et al noted a higher incidence of bradycardia (heart rate <80 beats/min) in the hypothermia group compared with the normothermia group (11 vs 2 patients; \(P = .005\)). One study that reported a higher incidence of arrhythmia also reported that none of the infants had major arrhythmia (requiring intervention). Thrombocytopenia did not result in adverse consequences in any infant. No significant between-group differences were observed in adverse effects or organ dysfunction.

**SECONDARY OUTCOMES**

Subgroup analyses based on severity of encephalopathy (moderate or severe) revealed significant reduction in the risk of the combined outcomes of death or moderate to severe neurodevelopmental disability and severe cerebral palsy in patients with moderate encephalopathy in the hypothermia group compared with the control group (Table 3). In patients with severe encephalopathy, the trends were similar but did not reach statistical significance. Other a priori planned subgroup analyses were not performed at this stage because of the small number of studies and almost similar division of studies as subgroup analyses based on severity of insult. The absolute number of patients contributing to each meta-analysis from individual studies is given in Table 4.

**COMMENT**

In this systematic review of 8 eligible trials of acceptable quality, we identified that for neonatal postintrapartum asphyxial HIE, therapeutic hypothermia reduces the risk of the combined outcome of death or moderate to severe neurodevelopmental disability in infancy or childhood and individual outcomes of death, severe neurodevelopmental disability, severe cerebral palsy, and severe cerebral palsy.
### Table 1. Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Study or Subcategory</th>
<th>Treatment Group</th>
<th>Control Group, n/N</th>
<th>Favors Treatment Group</th>
<th>Favors Control Group</th>
<th>Weight, %</th>
<th>RR, Fixed (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akisu et al31</td>
<td>11/10</td>
<td>12/10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gunn et al32</td>
<td>108/110</td>
<td>32/30</td>
<td>20/15</td>
<td>32/33</td>
<td>100.00</td>
<td>0.76 (0.65-0.88)</td>
</tr>
<tr>
<td>Gluckman et al30</td>
<td>14/27</td>
<td>21/25</td>
<td>13.54</td>
<td>0.62 (0.41-0.92)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lin et al33</td>
<td>59/108</td>
<td>73/110</td>
<td>44.90</td>
<td>0.82 (0.66-1.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bhat32</td>
<td>45/102</td>
<td>64/103</td>
<td>39.53</td>
<td>0.71 (0.54-0.95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shankaran et al14</td>
<td>9/10</td>
<td>102/106</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td></td>
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<td></td>
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</tr>
</tbody>
</table>

Abbreviations: BD, base deficit; NA, data not available; NP, nasopharyngeal; UA, umbilical arterial.

a All studies included infants with encephalopathy.

b Additional criteria required including acute perinatal event, Apgar score less than 5 at 10 minutes, or need for mechanical ventilation at age more than 10 minutes.

c All studies excluded infants with congenital anomalies.

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developmental indices (Mental Developmental Index and Psychomotor Developmental Index) less than 70, especially in patients with moderate encephalopathy. Patients in the hypothermia group had higher incidences of arrhythmia and thrombocytopenia; however, these were not clinically important.
Combined event rates. At least 3 multicenter RCTs of this intervention are ongoing but will not be completed for 3 years. Of these, the TOBY trial\textsuperscript{15} had a planned sample size of 400 patients; however, recruitment was stopped after enrollment of 325 patients. Simbruner\textsuperscript{16} has modified the protocol to include mildly asphyxiated patients (1-sided sample

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Studies</th>
<th>Events in Treatment Group, No. (%)</th>
<th>Events in Control Group, No. (%)</th>
<th>RR\textsuperscript{a} (95% CI)</th>
<th>RD\textsuperscript{a} (95% CI)</th>
<th>No. Needed to Treat/Harm (95% CI)</th>
<th>F Test of Heterogeneity for RR (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurodevelopmental disability in survivors\textsuperscript{12,30}</td>
<td>4</td>
<td>50/177 (28)</td>
<td>67/153 (44)</td>
<td>0.65 (0.48 to 0.87)</td>
<td>−0.16 (−0.26 to −0.05)</td>
<td>6 (4 to 20)</td>
<td>0 (0.55)</td>
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<tr>
<td>Severe cerebral palsy\textsuperscript{6,20}</td>
<td>2</td>
<td>29/149 (19)</td>
<td>40/132 (30)</td>
<td>0.64 (0.42 to 0.98)</td>
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<td>9 (5 to 100)</td>
<td>0 (0.92)</td>
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<tr>
<td>Mental Developmental Index \textless 70\textsuperscript{13,20,30}</td>
<td>3</td>
<td>44/162 (27)</td>
<td>53/135 (39)</td>
<td>0.69 (0.50 to 0.96)</td>
<td>−0.12 (−0.23 to −0.01)</td>
<td>8 (4 to 100)</td>
<td>0 (0.84)</td>
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<td>Psychomotor Developmental Index \textless 70</td>
<td>3</td>
<td>45/160 (28)</td>
<td>52/129 (40)</td>
<td>0.70 (0.50 to 0.96)</td>
<td>−0.12 (−0.23 to −0.01)</td>
<td>8 (4 to 100)</td>
<td>0 (0.40)</td>
</tr>
</tbody>
</table>

Table 2. Secondary Effectiveness and Safety Outcomes: Hypothermia vs Control Groups

Abbreviations: CI, confidence interval; NS, not significant; PPHN, persistent pulmonary hypertension of the newborn; RD, risk difference; RR, relative risk.

\textsuperscript{a} Calculated based on the inverse variance method (weight given to each study is chosen to be the inverse of the variance of the effect estimate) and not simply combined event rates.

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</tr>
</tbody>
</table>

Table 3. Subgroup Analysis According to Severity of Encephalopathy

Abbreviations: CI, confidence interval; RD, risk difference; RR, relative risk.

\textsuperscript{a} Calculated based on the inverse variance method (weight given to each study is chosen to be the inverse of the variance of the effect estimate) and not simply combined event rates.

\textsuperscript{b} Number needed to treat: 6 (95% CI, 4 to 20).

\textsuperscript{c} Number needed to treat: 6 (95% CI, 3 to 50).

A Cochrane review concluded that evidence is lacking to make recommendations based on the data available in 2003.\textsuperscript{13} At least 3 multicenter RCTs of this intervention are ongoing\textsuperscript{27,33,30} but will not be completed for 3 years. Of these, the TOBY trial\textsuperscript{15} had a planned sample size of 400 patients; however, recruitment was stopped after enrollment of 325 patients. Simbruner\textsuperscript{16} has modified the protocol to include mildly asphyxiated patients (1-sided sample


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other neuroprotective interventions. Saugstad indicated the equipoise of ongoing trials and suggested taking outcomes from 2 methods of hypothermia (systemic and selective head cooling) may be criticized; however, they precluded generalized use sparing outcomes for each study contributing to outcomes.a

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Aksu et al10</th>
<th>Gunn et al12</th>
<th>Gluckman et al29</th>
<th>Lin et al30</th>
<th>Bhat2</th>
<th>Eicher et al29,30</th>
<th>Shankaran et al31</th>
<th>Shankaran et al32</th>
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</thead>
<tbody>
<tr>
<td>Moderate to severe neurodevelopmental disability in survivor</td>
<td>NA</td>
<td>2/12 vs 1/10</td>
<td>23/72 vs 31/68</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>4/17 vs 7/11</td>
<td>NA</td>
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<tr>
<td>Severe cerebral palsy</td>
<td>NA</td>
<td>NA</td>
<td>14/72 vs 21/68</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>15/77 vs 19/64</td>
<td>NA</td>
</tr>
<tr>
<td>Mental Developmental Index &lt; 70</td>
<td>NA</td>
<td>NA</td>
<td>21/70 vs 24/61</td>
<td>NA</td>
<td>NA</td>
<td>4/17 vs 5/12</td>
<td>19/75 vs 24/62</td>
<td>NA</td>
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<tr>
<td>Psychomotor Developmental Index &lt; 70</td>
<td>NA</td>
<td>NA</td>
<td>21/69 vs 23/56</td>
<td>NA</td>
<td>NA</td>
<td>4/17 vs 7/11</td>
<td>20/74 vs 22/62</td>
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<tr>
<td>Severe visual deficit</td>
<td>NA</td>
<td>NA</td>
<td>7/72 vs 11/64</td>
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<td>NA</td>
<td>2/17 vs 11/11</td>
<td>5/75 vs 9/63</td>
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<tr>
<td>Severe hearing deficit</td>
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<td>1/17 vs 1/11</td>
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<tr>
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<td>11/72 vs 11/67</td>
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<td>1/17 vs 0/11</td>
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<td>NA</td>
<td>5/32 vs 7/33</td>
<td>12/102 vs 27/106</td>
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<tr>
<td>Death</td>
<td>0/11 vs 2/10</td>
<td>2/12 vs 2/10</td>
<td>36/108 vs 42/110</td>
<td>2/31 vs 2/30</td>
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<td>29/72 vs 31/64</td>
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<tr>
<td>Arrhythmia</td>
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<td>10/112 vs 1/118</td>
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<td>NA</td>
<td>2/102 vs 1/106</td>
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<td>Hypotension</td>
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<td>4/102 vs 35/106</td>
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<tr>
<td>Coagulopathy</td>
<td>NA</td>
<td>NA</td>
<td>21/112 vs 17/118</td>
<td>NA</td>
<td>NA</td>
<td>19/31 vs 18/11</td>
<td>18/102 vs 12/106</td>
<td>NA</td>
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<tr>
<td>Thrombocytopenia</td>
<td>NA</td>
<td>3/12 vs 2/10</td>
<td>36/112 vs 26/118</td>
<td>NA</td>
<td>NA</td>
<td>20/31 vs 12/31</td>
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<tr>
<td>Oliguria</td>
<td>NA</td>
<td>12/12 vs 10/10</td>
<td>73/112 vs 83/118</td>
<td>NA</td>
<td>NA</td>
<td>27/31 vs 28/31</td>
<td>16/102 vs 23/106</td>
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<tr>
<td>Liver dysfunction</td>
<td>NA</td>
<td>NA</td>
<td>42/112 vs 3/118</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>10/202 vs 16/106</td>
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<td>PPHN</td>
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<td>NA</td>
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<td>9/31 vs 5/31</td>
<td>25/102 vs 23/106</td>
<td>NA</td>
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<tr>
<td>Hypoglycemia</td>
<td>2/11 vs 2/10</td>
<td>5/12 vs 2/10</td>
<td>14/112 vs 20/118</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>12/102 vs 16/106</td>
<td>NA</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>NA</td>
<td>6/12 vs 5/10</td>
<td>71/112 vs 73/118</td>
<td>NA</td>
<td>NA</td>
<td>9/31 vs 9/31</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Seizures</td>
<td>0/11 vs 3/10</td>
<td>7/12 vs 4/10</td>
<td>93/112 vs 96/118</td>
<td>NA</td>
<td>NA</td>
<td>7/31 vs 0/31</td>
<td>31/102 vs 28/106</td>
<td>NA</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1/11 vs 2/10</td>
<td>0/12 vs 1/10</td>
<td>3/112 vs 3/118</td>
<td>NA</td>
<td>NA</td>
<td>1/31 vs 0/31</td>
<td>5/102 vs 6/106</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: NA, data not available; PPHN, persistent pulmonary hypertension of the newborn.

aValues are given as treatment event rate/total in treatment group (assessed) vs control event rate/total in control group (assessed) for respective outcome.

size of 150 patients). Since the study by Shankaran et al,9 hypothermia is offered as the standard of care in centers (part of the National Institute of Health Child Health and Human Development [NIHCHD] network) that participated in the study. Paradoxically, in a recently concluded consensus conference organized by the NIHCHD, the panel identified that the major limitation in the evaluation of hypothermia for neuroprotection was the lack of long-term safety and efficacy data and cautioned against the use of hypothermia.17,38,39 In another review, Edwards and Azzopardi10 performed a (speculative) meta-analysis of 3 studies,29,30 and identified similar estimates (RR, 0.76; 95% CI, 0.65-0.89) for death or neurodevelopmental disability; however, they precluded generalized use sparing the result of their own and other trials. Thoresen and Whitelaw,41 reviewing the same 3 studies,9,29,30 questioned the equipoise of ongoing trials and suggested taking the next step in research, combining hypothermia with other neuroprotective interventions. Saugstad39 indicated that plans are forthcoming for combining hypothermia with resuscitation in room air in infants with asphyxia. The pragmatic aspects of implementation of hypothermia need to be developed in the local context. The careful use of devices such as a cooling blanket may provide initial hypothermia until the arrival of a transport team for transfer where ongoing care can be provided in accordance with protocol.

A meta-analysis is as good as the individual studies that it includes. Failure to conduct meta-analyses can delay introduction of effective treatments; however, they are prone to several biases. Of the 8 studies included in our review, 2 were large, multicenter, international RCTs,9,30,31 3 were moderate-sized national RCTs,8,29,33; and 3 were pilot single-unit studies.13,14,32 There were clinical heterogeneities among these studies in inclusion criteria, severity of illness, degree of hypothermia, and outcomes assessment. However, all neonates had evidence of HIE. Only 1 study used amplitude-integrated encephalography for study enrollment,30 which is not surprising because of the limited availability of the instrument and expertise. Combining outcomes from 2 methods of hypothermia (systemic and selective head cooling) may be criticized; however, our subgroup analyses reveal that the direction of effect in both interventions was toward improvement in the primary outcome. In addition, selective head cooling also induces mild systemic hypothermia.

Outcome assessment is a concern in trials of hypothermia because of the inability to mask hypothermia therapy and the possible implications for decision making about life support. Common practice is to use combined outcomes in postasphyxial HIE because most deaths are secondary to withdrawal of life-sustaining medical treatment. Critics predicted, and it has been confirmed, that parents of infants in the intervention group would be less likely to be offered and less likely to accept withdrawal of life support than parents of infants in the control group. However, neurodevelopmental disability rate was reduced in the hypothermia group, refuting the notion of physician bias against withdrawal of life support.
The strengths of our meta-analysis include reports from 8 RCTs performed worldwide and an exhaustive literature search with no language restriction. We caution readers about interpretations of subgroup analyses. Inasmuch as these are only hypotheses generating, the differences observed could simply be the result of differences in the studies, and we have not performed any direct statistical comparisons.

Our results reveal significant improvement in the composite outcome in survivors who received hypothermia. We examined how many more infants would be needed to nullify the positive effect (RR of death or moderate to severe neurodevelopmental disability, 0.76; 95% CI, 0.65-0.88) and cause the upper margin of this CI to cross 1. Hypothetically, if all future trials produce a composite adverse outcome rate of 65% in both groups (similar to the control group of included studies), that is, no effect on hypothermia, then more than 1500 additional infants would be needed. This is not even close to the combined total number of patients planned in the ongoing 3 RCTs (approximately 800 infants). This theoretical analysis is not intended to limit recruitment in ongoing trials; however, it alerts those awaiting the results. The overall results of this meta-analysis and reported RCTs seriously question the equipoise of these trials and support the recent call for a review of the topic.44

Possible reservations to these results are related to age at assessment of the outcome (12-24 months) and adverse effects. Shankaran et al45 reported that in these patients, neurologic examination at 12 months can predict severe disability at age 5 years. We acknowledge that long-term safety data are lacking; however, reduction in mortality without increase in the number of infants with substantial early-onset neurodevelopmental disability is a finding difficult to ignore. Bradycardia is common with hypothermia, as tachycardia is with fever. Thrombocytopenia associated with hypothermia is in keeping with the physiologic response of reduced coagulability observed in hibernating animals; otherwise, their circulatory system would become clogged.46

With a 16% risk reduction in primary outcome, we calculate that in the United States alone (+4 million annual births), this could potentially prevent death or severe disability in 1200 neonates per year, or at least 3 neonates per day. On the basis of findings in this review, we suggest hypothermia for the treatment of postintrapartum asphyxial HIE within the first 6 hours after birth, in particular in infants with moderate encephalopathy being treated in centers with expertise and within the strict guidelines outlined in the protocols of these studies. Parents need to be informed about the known reductions in short-term adverse outcomes and the lack of long-term safety data. We strongly advocate continued follow-up of the infants enrolled in these trials to ascertain the long-term effects of hypothermia in survivors. Further research to answer questions such as ideal time of initiation of intervention, duration of intervention, degree of hypothermia, method of hypothermia, duration of rewarming, and ideal candidates for this intervention is needed.


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