Supplementary Online Content


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This supplementary material has been provided by the authors to give readers additional information about their work.
eFigure 1. Flow diagram of study selection.

395 records identified through data base searching from June 2007 – May 2011

8 records identified through the 2007 Cochrane systematic review search<sup>1</sup>

313 records after duplicates removed

313 records screened

299 Records excluded by title or abstract

14 full-text articles assessed for eligibility

7 full text articles excluded:
- 6 (incomplete follow up data)
- 1 (significant methodological limitations)

7 studies included in the quantitative synthesis (meta-analysis)
**eFigure 2. Forest plot of the primary outcome excluding the trial by Zhou et al**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hypothermia</th>
<th>Normothermia</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
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<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Azzoparadi 2009</td>
<td>74</td>
<td>163</td>
<td>86</td>
<td>162</td>
</tr>
<tr>
<td>Gluckman 2005</td>
<td>59</td>
<td>108</td>
<td>73</td>
<td>110</td>
</tr>
<tr>
<td>Gunn 1998</td>
<td>7</td>
<td>18</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>Jacobs 2011</td>
<td>51</td>
<td>91</td>
<td>58</td>
<td>78</td>
</tr>
<tr>
<td>Shankaran 2005</td>
<td>45</td>
<td>102</td>
<td>64</td>
<td>103</td>
</tr>
<tr>
<td>Simbruner 2010</td>
<td>27</td>
<td>53</td>
<td>48</td>
<td>58</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>535</strong></td>
<td><strong>524</strong></td>
<td><strong>263</strong></td>
<td><strong>333</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \chi^2 = 4.88, \ df = 5 \ (P = 0.43); \ I^2 = 0\%

Test for overall effect: \( Z = 4.66 \ (P < 0.00001) \)
eFigure 3. Forest plot of the primary outcome in infants with moderate HIE excluding the trial by Zhou et al.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hypothermia</th>
<th>Normothermia</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
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<tr>
<td></td>
<td>Events</td>
<td>Total Events</td>
<td>Weight</td>
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<tr>
<td>Azzoparadi 2009</td>
<td>20</td>
<td>65</td>
<td>30</td>
<td>67</td>
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<tr>
<td>Gluckman 2005</td>
<td>28</td>
<td>62</td>
<td>39</td>
<td>69</td>
</tr>
<tr>
<td>Gunn 1998</td>
<td>4</td>
<td>10</td>
<td>1</td>
<td>5</td>
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<td>Jacobs 2011</td>
<td>26</td>
<td>61</td>
<td>34</td>
<td>51</td>
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<td>Shankaran 2005</td>
<td>22</td>
<td>69</td>
<td>30</td>
<td>63</td>
</tr>
<tr>
<td>Simbruner 2010</td>
<td>6</td>
<td>19</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>286</td>
<td>270</td>
<td>100.0%</td>
<td>0.70</td>
</tr>
</tbody>
</table>

Total events: 106 | 143

Heterogeneity: Chi² = 2.55, df = 5 (P = 0.77); I² = 0%
Test for overall effect: Z = 3.72 (P = 0.0002)
**eFigure 4. Forest plot of the primary outcome in infants with severe HIE excluding the trial by Zhou et al.**

<table>
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<tr>
<th>Study or Subgroup</th>
<th>Hypothermia</th>
<th>Normothermia</th>
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</thead>
<tbody>
<tr>
<td>Azzoparadi 2009</td>
<td>54</td>
<td>98</td>
<td>30.8%</td>
<td>0.93 [0.73, 1.19]</td>
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<tr>
<td>Gluckman 2005</td>
<td>28</td>
<td>40</td>
<td>35</td>
<td>18.5%</td>
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<tr>
<td>Gunn 1998</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>1.9%</td>
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<tr>
<td>Jacobs 2011</td>
<td>25</td>
<td>30</td>
<td>27</td>
<td>13.7%</td>
</tr>
<tr>
<td>Shankaran 2005</td>
<td>23</td>
<td>32</td>
<td>40</td>
<td>16.4%</td>
</tr>
<tr>
<td>Simbruner 2010</td>
<td>21</td>
<td>34</td>
<td>43</td>
<td>18.7%</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>237</strong></td>
<td><strong>243</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.84 [0.75, 0.94]</strong></td>
</tr>
</tbody>
</table>

Total events: 153 [Hypothermia] 188 [Normothermia]

Heterogeneity: Chi² = 4.72, df = 5 (P = 0.45); I² = 0%

Test for overall effect: Z = 3.03 (P = 0.002)
Characteristics of included studies [ordered by study ID]
(See Cochrane review “Cooling for newborns with hypoxic ischaemic encephalopathy” for the characteristics of the included studies before June 2007).

Azzopradi 2009

Methods
Multi-centre RCT.
Blinding of randomization: Adequate; assignment to a treatment group was performed by means of central telephone randomization or a secure Web-based system.
Blinding of intervention: Not possible, with care givers aware of treatment allocation.
Blinding of outcome measurement: Uncertainty about masking of short-term outcome assessors, but assessors of 18 month neurodevelopmental outcome masked to treatment group assignment.
Follow up: 18 month follow-up in 323/325 (99%).

Participants
325 infants born at >=36 weeks gestation WITH clinical evidence of peripartum hypoxia-ischemia (they also had to have, at 10 minutes after birth, either an Apgar score of 5 or less or a continued need for resuscitation or, within 60 minutes after birth, acidosis (defined as any occurrence of umbilical- cord, arterial, or capillary pH of <7.00 or base deficit of ≥16 mmol per litre)).
AND, they had to have moderate-to-severe encephalopathy (indicated by lethargy, stupor, or coma) and either hypotonia, abnormal reflexes (including oculomotor or pupillary abnormalities), an absent or weak suck, or clinical seizures.
AND, they had to have abnormal background activity of at least 30 minutes’ duration or seizures on amplitude integrated electroencephalography.
Excluded infants were expected to be more than 6 hours of age at the time of randomization and those with major congenital abnormalities known at randomization that required surgery or were suggestive of chromosomal anomaly or syndromes that involve brain dysgenesis.

Interventions
Hypothermia (n=163): In incubators with the power turned off with a cooling blanket in which fluid was circulated whose temperature was regulated by a manually adjusted thermostat (Tecotherm TS 200, Tec-Com). The target rectal temperature was 33 to 34°C for 72 hours.
Control treatment (n=162): radiant heaters or in incubators, which were servo-controlled according to the abdominal skin temperature to maintain the rectal temperature at 37.0 ± 0.2°C.

Outcomes
Primary: composite of death or severe neurodevelopmental disability in survivors at 18 months of age. Severe neurodevelopmental disability was defined as a score of less than 70 on the Mental Developmental Index of the Bayley Scales of Infant Development II (BSID-II) (2 on which the standardization mean [±SD] is 100±15 and higher scores indicate better performance), a score of 3 to 5 on the Gross Motor Function Classification System (GMFCS) (3), or bilateral cortical visual impairment with no useful vision.
Secondary: Adverse outcomes included intracranial hemorrhage, persistent hypotension, pulmonary hemorrhage, pulmonary hypertension, prolonged blood coagulation time, culture-proven sepsis, necrotizing enterocolitis, cardiac arrhythmia, thrombocytopenia, major venous thrombosis, renal failure treated with dialysis, pneumonia, pulmonary air leak, and duration of hospitalization.
Secondary outcomes at 18 months included death and severe neurodevelopmental disability, the score on the Psychomotor Developmental Index of BSID-II, cerebral palsy, hearing loss, seizures treated with anticonvulsant agents, microcephaly (i.e., age- and sex-standardized head circumference of more than 2 SD below the mean), multiple...
neurodevelopmental abnormalities (i.e., more than one of the following: a GMFCS score of 3 to 5, \(^3\) a score of <70 on the Mental Developmental Index of BSID-II, \(^2\) seizures, or cortical visual impairment and hearing loss), and survival without neurologic abnormality (i.e., a Mental Developmental Index score >84, a Psychomotor Developmental Index score >84, no abnormalities on GMFCS assessment, \(^3\) and normal vision and hearing).

**Notes**

Minimization was used to ensure balance of treatment assignment among infants with various grades of abnormality on amplitude-integrated electroencephalography and within each participating center. All infants underwent sedation with morphine infusions or with chloral hydrate if they appeared to be distressed. Re-warmed at no more than 0.5 °C per hour to a maximum of 37±0.2°C. Death occurred after the withdrawal of care in 34 of the 39 (87%) in the cooled group and 29 of the 39 (74%) in the non-cooled group. Additional information was obtained from the author.

**Risk of bias**

<table>
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<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A – Adequate</td>
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</table>

**Jacobs 2011**

**Methods**

Multi-centre international RCT. Blinding of randomization: Adequate; Assignment to treatment group was by sequentially numbered, sealed opaque envelopes containing computer generated random numbers in a 1:1 ratio with variable block sizes. Blinding of intervention: Not possible, with care givers aware of treatment allocation. Blinding of outcome measurement: Uncertainty about masking of short-term outcome assessors, but assessors of 2 years neurodevelopmental outcome masked to treatment allocation.

Follow up: 2 years follow-up in 208/221 (94%).

**Participants**

221 infants born at >=35 weeks gestation with moderate or severe encephalopathy defined according to modified Sarnat criteria (lethargy, stupor, coma, abnormal tone, and/or seizures). \(^4\) AND indicators of peripartum hypoxia-ischemia [at least 2 of the following clinical characteristics: an Apgar score of 5 or less at 10 minutes, continued need for mechanical ventilation at 10 minutes, and/or metabolic acidosis (cord pH< 7.00; an arterial, venous, or capillary pH < 7.00; or a base deficit of ≥ 12 within 60 minutes of birth)].

Infants were excluded if hypothermia could not start within 6 hours of birth, if the birth weight was less than 2 kg, if major congenital abnormalities were suspected, if there was overt bleeding, if the infant required more than 80% inspired oxygen, if death was imminent (refractory hypotension or acidosis unresponsive to treatment), or if therapeutic hypothermia had commenced before assessment.

**Interventions**

Hypothermia (n=110): Hypothermia to the target core temperature of 33.5°C (range, 33°C- 34°C) was achieved by turning the radiant warmer (or transport incubator) off and exposing the infant to the ambient temperature. Two refrigerated gel packs were applied across the chest and/or under the head and shoulders if the temperature was above 35.5°C at initiation of hypothermia and sequentially removed when the temperature fell below 35°C and then 34.5°C. The radiant warmer heater output (or transport incubator temperature) was manually adjusted every 15 to 30 minutes if the temperature was below 33.5°C. Gel packs were also applied when the temperature was above 34.0°C during the maintenance period of hypothermia between 6 and 72 hours after

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randomization.  
Control treatment (n=111): under a radiant warmer with their core temperature maintained at 37°C (range, 36.8°C- 37.3°C) for the 72-hour.

Outcomes

Primary: composite outcome was mortality or major sensorineural disability at 2 years of age. Major sensorineural disability comprised neuromotor delay (cerebral palsy [CP] in which the child was not walking [moderate CP] or was unlikely to walk [severe CP] at 2 years, a Psychomotor Development Index score on the Bayley Scales of Infant Development II [BSID-II] of less than −2 SDs, 2 a Motor Composite Scale score on the BSID-III of less than −2 SDs, 5 or a disability level on the Gross Motor Function Classification System [GMFCS] of 2-5), 6 developmental delay (a Mental Development Index score on the BSID-II of less than −2 SDs or a Cognitive Scale score or a Language Composite Scale score on the BSID-III of less than −2 SDs), 5 blindness (vision worse than 20/200 in both eyes), and/or deafness requiring amplification or worse (ie, the infant does not respond to amplification and is in need of a cochlear implant). 6 2  
Secondary outcomes at 2 years included mortality, major sensorineural disability and its individual components (neuromotor delay, developmental delay, blindness, deafness requiring amplification, or worse), and survival free of any sensorineural disability (no neuromotor delay [no CP or a GMFCS disability level of 0] and a BSID-II Psychomotor Development Index of greater than −1 SD or a BSID-II Motor Composite Scale score of greater than −1 SD], 6 5 no developmental delay [a BSID-II Mental Development Index score of greater than −1 SD or BSIDIII Cognitive and Language Composite Scale scores of greater than −1 SD], no blindness, and no deafness). 6 2 5 Adverse effects and outcomes from therapeutic hypothermia included any cardiac arrhythmia that required medical treatment, prolonged QT interval (> 98th centile for heart rate and age 7), hypotension treated with inotropes, overt bleeding, thrombosis or coagulopathy treated with fresh frozen plasma and/or cryoprecipitate, hypoxia in 100% inspired oxygen that resulted in the hypothermia regimen being discontinued, thrombocytopenia (platelet count, < 150 x10^3/μL, oliguria (urine output, < 1.0 mL/kg/h on day 2 or day 3), hepatic dysfunction (alanine aminotransferase level,> 100 U/L, rectal bleeding or necrotizing enterocolitis, sepsis, and mortality.

Notes

Recruitment was stopped by the ICE steering committee on July 27, 2007, on the basis of accumulating external evidence in favour of hypothermia with loss of equipoise. Outborn infants were identified at the time of referral (at the birth hospital) by either a study investigator or a member of the retrieval team who had received education about the ICE trial. Inborn infants were assessed for eligibility by site investigators in participating NICUs.  
Re-warming was over 8 to 12 hours by 0.5°C every 2 hours. Decisions to withdraw treatment were made by the clinical team independent of the trial. There was no significant difference in core temperature between inborn and outborn infants. 
A total of 64 infants had at least 1 core temperature reading that was below 33°C in the hypothermia group and 2 infants in the control group with a core temperature reading ranging from 32.7°C to 32.9°C. 
Sixteen control infants had a temperature of 38.0°C or higher at some stage, which was associated with a trend toward increased mortality. Therapeutic hypothermia was discontinued in 6 infants. Three infants had overt bleeding, 1 was withdrawn from the study at parental request, and 2 were withdrawn by clinicians. 
Fifteen survivors were assessed with the BSID-III, the scores of BSID-III were not pooled and developmental delay on BSID-III scores was categorized according to published data from Australian normal-birth weight term infants at 2 years of age. 8
There were 6 survivors who were assumed to have normal cognition and were therefore normal for the primary outcome. They were assessed as “normal” at 2 years on neurodevelopmental assessment for motor, visual, and auditory outcome but who did not have the Bayley motor or cognitive assessments performed. Another 6 survivors with missing data of GMFCS disability level were considered to have normal motor outcome (because none had CP or psychomotor delay measured on the Bayley score). There was a protocol violation by including 19% of infants with mild HIE (15% in the cooled group and 23% in the control group).

End-of-life discussions preceded 65 of 69 deaths (94.2%), with decisions made to withdraw life-sustaining treatment and provide palliative management (for 22 of 27 cooled infants [81.5%] and 30 of 42 control infants [71.4%]) or to not escalate treatment (for 4 of 27 cooled infants [14.8%] and 9 of 42 control infants [21.4%]).

<table>
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<tr>
<td></td>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A – Adequate</td>
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</table>

Simbruner 2010

Methods

Multi-centre international RCT.
Blinding of randomization: Adequate, with block randomization by using sealed envelopes stratified by centre and severity of HIE (moderate or severe) with the aim of starting no more than 6 hours after birth.
Blinding of intervention: Not possible, with caregivers aware of treatment allocation
Blinding of outcome measurement: Uncertainty about masking of short-term outcome assessors, but assessors of 18 month neurodevelopmental outcome masked to treatment group assignment.
Follow up: 18 month follow-up reported in 111/129 (86%).

Participants

129 infants born at $\geq 36$ weeks gestation WITH clinical evidence of birth asphyxia [Apgar score of $< 5$ at 10 min after birth, continued need for resuscitation (including endotracheal intubation or mask ventilation) at 10 min after birth, umbilical cord pH or any arterial pH of $<7.00$ within 60 min after birth, or base deficit of $>16$ mmol/L within 60 min after birth
AND clinical evidence of encephalopathy with lethargy, stupor, or coma and $> = 1$ of following: hypotonia, abnormal reflexes (including oculomotor or pupillary abnormalities), absent or weak suck, or clinical seizures
AND abnormal standard EEG or aEEG findings
Excluded infants were $> 5.5$ hours of age at time of random assignment, received high-dose anticonvulsant therapy (phenobarbitone at $> 20$ mg/kg), birth weight of $< 1800$ g, gestational age of $< 36$ wk, head circumference of $< 3rd$ percentile for gestational age if birth weight and length are $> 3rd$ percentile, major congenital malformations with poor developmental prognosis, imperforate anus, gross hemorrhage or infant “in extremis”

Interventions

Hypothermia (n=64): water-perfused cooling mattress (Tecotherm TS Med 200 [Tec-Com, Halle, Germany]) for 72 hours. A rectal temperature was maintained 33.5 °C (range: 33.0–34.0 °C)
Control treatment (n=65): an open care unit. Body temperature was measured as rectal temperature of 37 °C [range: 36.5–37.5 °C]) for 72 hours.

Outcomes

Primary: combined death or severe disability (neurologic deficit with a functional score of 3 to 5, as defined by Palisano et al, 6 a development quotient of $< 2$ SD, a severe bilateral cortical visual deficit, or any combination of the aforementioned findings) at postnatal age of 18 to 21 months.
Secondary: death or severe disability by the severity of HIE, death, developmental
Primary outcomes include temperature, neurodevelopmental assessment at 18 months, and mortality. Secondary outcomes also include adverse events including mortality, arrhythmia, hypotension, overt bleeding, coagulopathy, thrombocytopenia, systemic infection, hemoconcentration, hypoglycemia, hypocalcaemia, bone marrow depression, abnormal liver function, metabolic acidosis, clinical seizures or on aEEG or EEG, intracranial hemorrhage, major venous thrombosis, initiation of ventilatory support after beginning of intervention or death during the intervention period.

**Notes**
- Terminated earlier than planned for ethical consideration
- All infants received morphine (0.1mg/kg) every 4 hours or an equivalent dose of fentanyl.
- Re-warmed at no more than 0.5 °C per hour.
- 14% underwent randomization and were lost to follow up (excluded in the final analysis)
- Sponsored by the Deutsche Forschungsgemeinschaft.
- Additional information was obtained from the author.

### Risk of bias

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<tr>
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<th>Authors’ judgement</th>
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<td>Allocation concealment?</td>
<td>Yes</td>
<td>A – Adequate</td>
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</table>

**Zhou 2010**

**Methods**

- Multi-centre RCT.
- Blinding of randomization: Adequate; codes were generated by a computer and supplied in numbered, sealed opaque envelopes. Assignments were stratified according to centre in a randomized block design with a block size of 6.
- Blinding of intervention: Not possible, with care givers aware of treatment allocation.
- Blinding of outcome measurement: Uncertainty about masking of short-term outcome assessors, but assessors of 18 month neurodevelopmental outcome masked to treatment group assignment.
- Follow up: 18 month follow-up in 194/235 (83%).

**Participants**

- 235 infants born at ≥37 weeks gestation and birth weight ≥2500 g WITH clinical evidence of exposure to perinatal hypoxia-ischemia (an Apgar score ≤3 at 1 minute and ≤5 at 5 minutes; cord blood gas pH <7.0 or base deficit ≤16 mmol/L; and need for resuscitation or ventilation at 5 minutes of age).
- AND mild, moderate, or severe encephalopathy (Sarnat criteria) by a certified examiner, including lethargy, stupor, or coma, with 1 or more of the findings of hypotonia, abnormal reflexes, or clinical seizure.
- Exclusion criteria were as follows: (1) Major congenital abnormalities; (2) Infection (rupture of membranes >18 hours or maternal fever >38 °C or amniotic fluid foul smell); (3) Other encephalopathy (neonatal stroke, central nervous system abnormality, intracranial hemorrhage diagnosed by CT or head ultrasonography); (4) Severe anemia (hemoglobin <120 g/L).

**Interventions**

- Hypothermia (n=119): head cooling by a semiconductor controlled water circulation cooling device (YJW608-04B; Henyang Radio Manufactory, Hunan, China). The temperature probe was placed in the nasopharynx to maintain the nasopharyngeal temperature at (34 ± 0.2 C). Infants were nursed under a radiant warmer, which was servo controlled to the infant’s abdominal skin temperature and adjusted to maintained rectal temperature at 34.5° to 35°C. Head cooling was started within 6 hours of age and continued for 72 hours, followed by spontaneous re-warming.
- Control treatment (n=116): radiant warmer servo-controlled to infant’s abdominal skin.
Outcomes

Primary: combined endpoint of death and severe disability at 18 months of age. GMFCS level 3-5 or DQ <70 (on Gesell Child Development Scale score) were defined as severe disability. Secondary: major adverse events [severe arrhythmia (second or third degree A-V block or atrial or ventricular arrhythmia), major venous thrombosis (ie, thrombosis of a major vessel not related to an infusion line), refractory hypotension (mean blood pressure less than 40 mm Hg despite full support), moderate or severe scleredema (greater or equal to 20% body surface area), and severe bleeding (disseminated intravascular coagulation, lung hemorrhage, gastrointestinal hemorrhage and gross hematuria)], common adverse events (mild arrhythmia (sinus bradycardia if heart rate <80 beats/min, prolonged QT interval, occasional premature beats, and first degree A-V block), mild scleredema (less than 20% body surface area), renal dysfunction (creatinine >120 mmol/L, blood urea nitrogen >8 mmol/L or urine output <1 mL/kg/h), liver dysfunction (alanine transaminase >100 U/L), thrombocytopenia (platelet <100 x 10^9/L), serum electrolytes or biochemical abnormalities (sodium <130 mmol/L or >150 mmol/L, potassium <3.5 mmol/L or >5.5 mmol/L, calcium <2.0 mmol/L, blood glucose >8 mmol/L or <2.6 mmol/L).

Notes

Spontaneous re-warming. The average time to reach 36.5 °C for rectal temperature was 12.5 ± 6.1 hours. There were no adverse events during the re-warming period. Included more males (87% in the selective head cooling group and 83% in the control group).

For infants who did not return for follow-up, information on neurodevelopment outcomes was assessed by trained pediatricians in a local child health care or rehabilitation department.

17% of the sample underwent randomization but were lost to follow up and excluded in the final analysis.

For those who lost to follow up (17%) it was not stated to which group they belonged (mild, moderate or severe groups).

Not stated if deaths followed withdrawal of care. Causes of death were explained in a table but were not clear.

Additional information was obtained from the author.

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References


