Hypothermia for Neonatal Hypoxic Ischemic Encephalopathy

An Updated Systematic Review and Meta-analysis

Mohamed A. Tagin, MB BCh; Christy G. Woolcott, PhD; Michael J. Vincer, MD; Robin K. Whyte, MB; Dora A. Stinson, MD

Objective: To establish the evidence of therapeutic hypothermia for newborns with hypoxic ischemic encephalopathy (HIE).

Data Sources: Cochrane Central Register of Controlled Trials, Oxford Database of Perinatal Trials, MEDLINE, EMBASE, and previous reviews.

Study Selection: Randomized controlled trials that compared therapeutic hypothermia to normothermia for newborns with HIE.

Intervention: Therapeutic hypothermia.

Main Outcome Measures: Death or major neurodevelopmental disability at 18 months.

Results: Seven trials including 1214 newborns were identified. Therapeutic hypothermia resulted in a reduction in the risk of death or major neurodevelopmental disability (risk ratio [RR], 0.76; 95% CI, 0.69-0.84) and increase in the rate of survival with normal neurological function (1.63; 1.36-1.95) at age 18 months. Hypothermia reduced the risk of death or major neurodevelopmental disability at age 18 months in newborns with moderate HIE (RR, 0.67; 95% CI, 0.56-0.81) and in newborns with severe HIE (0.83; 0.74-0.92). Both total body cooling and selective head cooling resulted in reduction in the risk of death or major neurodevelopmental disability (RR, 0.75; 95% CI, 0.66-0.85 and 0.77; 0.65-0.93, respectively).

Conclusion: Hypothermia improves survival and neurodevelopment in newborns with moderate to severe HIE. Total body cooling and selective head cooling are effective methods in treating newborns with HIE. Clinicians should consider offering therapeutic hypothermia as part of routine clinical care to these newborns.


GLOBAL ESTIMATES FOR ASphyxia-related neonatal deaths vary from 0.7 to 1.2 million annually. Peripartum asphyxia remains an important cause of long-term sensorineural impairments and disabilities.

During the last 2 decades, evidence from experimental and clinical studies suggests that therapeutic hypothermia reduces cerebral injury and improves neurological outcome. Experts and clinicians have been hesitant about these findings with the supposition that the evidence is yet insufficient to support widespread implementation of therapeutic hypothermia outside the limits of controlled trials. A Cochrane review of therapeutic hypothermia including 638 term newborns with moderate to severe encephalopathy and evidence of intrapartum asphyxia showed significant benefits in newborns with severe encephalopathy, but the benefits for newborns with moderate encephalopathy were unclear. Two more recent reviews showed significant benefits for newborns with moderate encephalopathy, but the benefits for newborns with severe encephalopathy were not signifi-
The primary objective of this review was to use all the available data, including those from the most recently published randomized trials, to evaluate the effectiveness of therapeutic hypothermia for newborns with hypoxic ischemic encephalopathy (HIE).

METHODS

DATA SOURCE

To identify all the relevant studies, the search strategy of the Cochrane systematic review, “Cooling for Newborns With Hypoxic Ischaemic Encephalopathy” (last edited in June 2007), was reproduced from June 2007 to May 2011. Relevant studies were identified from the Cochrane Central Register of Controlled Trials, the Oxford Database of Perinatal Trials, MEDLINE, and EMBASE using the following strategy: (Silver Platter—June 2007 to May 2011: Infant, Newborn (explode) [MeSH heading] and Asphyxia (explode) [MeSH heading] or Hypoxic Ischaemic Encephalopathy and Hypothermia (explode) [MeSH heading]). References from previous reviews were cross-referenced. No language restrictions were applied.

ELIGIBILITY CRITERIA

Randomized controlled trials that compared therapeutic hypothermia (either systemic or selective head cooling) to normothermia to treat newborns with HIE were included. Studies were selected only if they included data on death or disability at 18 months or older. Randomized controlled trials that had significant methodological limitations were excluded.

STUDY IDENTIFICATION AND DATA EXTRACTION

All titles and abstracts identified as potentially relevant by the literature search were assessed for inclusion in the review. The full texts for potentially eligible studies were reviewed against the predefined criteria. Data were extracted on a predefined data extraction form by the primary author (M.A.T.). The selection of relevant studies was by consensus. Whenever necessary, additional information and clarification of published data were requested from the authors of the individual trials.

CRITICAL APPRAISAL

The methodological quality of the studies was assessed using the risk of bias assessment tool as recommended by the Cochrane Neonatal Review Group except for the criterion of blinding of intervention (methods of cooling cannot be masked). The domains of assessment included sequence generation, allocation concealment, blinding of outcome assessment, completeness of assessment, selective reporting bias, and the likelihood of other biases. The methodological quality of the studies previously reported in the Cochrane review was reassessed.

OUTCOMES MEASURES

The primary outcome was a composite of death or long-term (≥18 months) major neurodevelopmental disability (cerebral palsy; developmental delay [<2 SDs] below the mean in Mental Developmental Index [MDI] score in Bayley Scales of Infant Development II [BSID-II]24 a Cognitive Scale score or a Language Composite Scale score on the BSID-III25,26 Griffiths assessment,26 Brunet-Lézine quotient,27 or Gesell Child Development Age Scale28; or intellectual impairment [IQ <2 SDs below mean], blindness [vision <6/60 in both eyes], or sensorineural deafness requiring amplification). Secondary outcomes included examining each component of the primary outcome independently, survival with normal neurological function (no cerebral palsy, normal development [not <1 SD below the mean on the aforementioned standardized tests], normal vision, and normal hearing). Furthermore, we determined if the severity of encephalopathy or the method of cooling modified the effect of hypothermia on the composite outcome of death or major disability. Grade of encephalopathy was assessed on the basis of clinical examination29 or amplitude-integrated electroencephalography (aEEG)30 both of which were considered equivalent.

DATA ANALYSIS

Meta-analysis was performed with Review Manager software (RevMan, version 5.0; Nordic Cochrane Centre) using the Mantel-Haenszel method and a fixed-effect model.19 Risk ratios (RRs) and the number needed to treat (NNT) with 95% CIs were calculated. The χ² test was applied to detect between-study heterogeneity, and P values were calculated to assess statistical heterogeneity.

RESULTS

Fourteen trials were evaluated for eligibility (eFigure 1; http://www.archpediatrics.com). Seven trials fulfilled the inclusion criteria; their details are shown in Table 1, with additional details noted in the eAppendix. The 7 studies that were excluded along with reasons for exclusion are shown in Table 2. Seven trials included mild HIE, 2 trials included moderate HIE, and 5 trials included severe HIE. The included trials were reported in the Cochrane review identified 9 randomized controlled trials7-10,12,32-34,36; only 3 trials reported data on death or major disability at 18 months or longer.10,12,32 Database searching between June 2007 and May 2011 identified 6 additional randomized controlled trials (eFigure 1; Table 1).13,20-22,35,37 Seven of the 14 trials reported data on death or major disability in their outcome. In fact, most newborns in this trial had severe disability (43 of 45 in the hypothermia group and 62 of 64 in the normothermia group either died or had an MDI of less than 70 at follow-up at 18-22 months). Therefore, the numbers reported in this trial for moderate or severe disability were used to define major disability in this review.

CLINICAL HETEROGENEITY ASSESSMENT AMONG INCLUDED STUDIES

A total of 1214 newborns with moderate to severe HIE were randomized in the included trials. Newborns who were reported to have mild HIE were excluded from this review. The included trials had similar enrollment criteria including evidence of birth asphyxia and moderate to severe HIE (Table 1). Three trials also included abnormal aEEG as an enrollment criterion. Newborns were at least 35 weeks gestation in 1 trial,10 at least 36 weeks in 4 trials,10,12,15,21 and at least 37 weeks in the other 2 trials. Four trials used total body cooling12,13,20,21 and 3 trials used selective head cooling with mild systemic hypothermia.10,22,23 In all the included trials,
random allocation and hypothermia were initiated within 6 hours after birth. Therapeutic hypothermia was maintained for 72 hours except in the trial by Gunn et al,\(^32\) in which cooling was discontinued between 48 and 72 hours if the newborn recovered neurologically. Rewarming was gradual at no more than 0.5°C per hour until the temperature was normalized in 5 trials\(^{10,12,13,20,21}\); passive rewarming was allowed in 1 trial.\(^{22}\) The rewarming process was unclear in the trial conducted by Gunn et al.\(^{32}\) Total body cooling was achieved either by cooling blankets placed under the newborns\(^{12,13,31}\) or by gel packs,\(^{20}\) and selective head cooling was achieved by a cooling cap\(^{10,22,32}\) (Table 1).

**Table 1. Details of Included Trials\(^a\)**

<table>
<thead>
<tr>
<th>Source</th>
<th>Characteristics</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azopradi et al,(^{10}) 2009</td>
<td>Inclusion</td>
<td>GA &gt;36 weeks with PHI, moderate to severe encephalopathy, and abnormal background on aEEG</td>
</tr>
<tr>
<td></td>
<td>Exclusion</td>
<td>Major congenital abnormalities or &gt;6 h of age</td>
</tr>
<tr>
<td></td>
<td>Intervention</td>
<td>Hypothermia group (n=163): cooling blanket to maintain rectal temperature 33°C-34°C</td>
</tr>
<tr>
<td></td>
<td>Control group (n=162): radiant heaters to maintain rectal temperature 37.0°C±0.2°C</td>
<td></td>
</tr>
<tr>
<td>Gluckman et al,(^{10}) 2005</td>
<td>Primary outcome</td>
<td>Death or severe neurodevelopmental disability in survivors at 18 mo of age</td>
</tr>
<tr>
<td></td>
<td>Inclusion</td>
<td>GA &gt;36 weeks with PHI, moderate to severe encephalopathy, and abnormal background on aEEG</td>
</tr>
<tr>
<td></td>
<td>Exclusion</td>
<td>Major congenital abnormalities, &gt;5.5 h of age, received prophylactic anticonvulsants, BW &lt;1800 g, HC &lt;2 SD for gestation if BW and length &gt;−2 SD, or critically ill and unlikely to benefit from intensive care</td>
</tr>
<tr>
<td></td>
<td>Intervention</td>
<td>Hypothermia group (n=116): cooling cap to maintain rectal temperature 34°C-35°C</td>
</tr>
<tr>
<td></td>
<td>Control group (n=118): radiant warmer to maintain rectal temperature 36.8°C-37.2°C</td>
<td></td>
</tr>
<tr>
<td>Gunn et al,(^{24}) 1998</td>
<td>Primary outcome</td>
<td>Death or severe encephalopathy in survivors at 18 mo of age</td>
</tr>
<tr>
<td></td>
<td>Inclusion</td>
<td>GA &gt;37 weeks with PHI and encephalopathy</td>
</tr>
<tr>
<td></td>
<td>Exclusion</td>
<td>Major congenital abnormality or metabolic diseases</td>
</tr>
<tr>
<td></td>
<td>Intervention</td>
<td>Hypothermia group (n=18): cooling cap with sequential randomization of rectal temperature to 36.0°C-36.5°C (n=6), then to 35.5°C-35.9°C (n=6), then to 34.5°C-35.4°C (n=6)</td>
</tr>
<tr>
<td></td>
<td>Control group (n=13): radiant warmer to maintain rectal temperature 36.8°C-37.2°C</td>
<td></td>
</tr>
<tr>
<td>Jacobs et al,(^{20}) 2011</td>
<td>Primary outcome</td>
<td>Acute adverse effects, long-term neurodevelopmental outcomes were also reported</td>
</tr>
<tr>
<td></td>
<td>Inclusion</td>
<td>GA &gt;35 weeks with PHI and moderate or severe encephalopathy</td>
</tr>
<tr>
<td></td>
<td>Exclusion</td>
<td>Major congenital abnormalities, &gt;6 h of age, BW &lt;2 kg, overt bleeding, required &gt;80% oxygen, death was imminent, or therapeutic hypothermia had commenced before assessment</td>
</tr>
<tr>
<td></td>
<td>Intervention</td>
<td>Hypothermia group (n=110): refrigerated gel packs to maintain rectal temperature 33°C-34°C</td>
</tr>
<tr>
<td></td>
<td>Control group (n=111): radiant warmer to maintain rectal temperature 36.8°C-37.3°C</td>
<td></td>
</tr>
<tr>
<td>Shankaran et al,(^{19}) 2005</td>
<td>Primary outcome</td>
<td>Mortality or major sensorineural disability in survivors at 2 y of age</td>
</tr>
<tr>
<td></td>
<td>Inclusion</td>
<td>GA &gt;36 weeks with PHI, &lt;6 h of age, and encephalopathy or seizures</td>
</tr>
<tr>
<td></td>
<td>Exclusion</td>
<td>Major congenital abnormalities, BW ≤ 1800 g, or &gt;6 h of age</td>
</tr>
<tr>
<td></td>
<td>Intervention</td>
<td>Hypothermia group (n=102): cooling blanket to maintain esophageal temperature 33°C-34°C</td>
</tr>
<tr>
<td></td>
<td>Control group (n=106): standard care to maintain esophageal temperature 36.5°C-37.0°C</td>
<td></td>
</tr>
<tr>
<td>Simbruner et al,(^{27}) 2010</td>
<td>Primary outcome</td>
<td>Death or moderate or severe disability in survivors at 18 to 22 mo of age</td>
</tr>
<tr>
<td></td>
<td>Inclusion</td>
<td>GA &gt;36 weeks, PHI, encephalopathy, and abnormal EEG or aEEG findings</td>
</tr>
<tr>
<td></td>
<td>Exclusion</td>
<td>Major congenital malformations, &gt;5.5 h of age, received anticonvulsant therapy, BW ≤ 1800 g, HC less than the third percentile for GA if BW and length are greater than the third percentile, imperforate anus, or gross hemorrhage</td>
</tr>
<tr>
<td></td>
<td>Intervention</td>
<td>Hypothermia group (n=64): cooling mattress to maintain rectal temperature 33°C-34°C</td>
</tr>
<tr>
<td></td>
<td>Control group (n=65): open care unit to maintain rectal temperature 36.5°C-37.5°C</td>
<td></td>
</tr>
<tr>
<td>Zhou et al,(^{22}) 2010</td>
<td>Primary outcome</td>
<td>Death or severe disability in survivors at 18 to 21 mo of age</td>
</tr>
<tr>
<td></td>
<td>Inclusion</td>
<td>GA ≥37 weeks, BW ≥ 2500 g, PHI, and encephalopathy</td>
</tr>
<tr>
<td></td>
<td>Exclusion</td>
<td>Major congenital abnormalities, signs of infection, other causes of encephalopathy or severe anemia</td>
</tr>
<tr>
<td></td>
<td>Intervention</td>
<td>Hypothermia group (n=119): cooling cap to maintain nasopharyngeal temperature 34°C±0.2°C and rectal temperature 34.5°C-35°C</td>
</tr>
<tr>
<td></td>
<td>Control group (n=116): radiant warmer to maintain rectal temperature 36.0°C-37.5°C</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: aEEG, amplitude-integrated electroencephalogram; BW, birth weight; EEG, electroencephalogram; GA, gestational age; HC, head circumference; PHI, periventricular hypoaxia-ischemia.

\(^a\)The included studies provided therapeutic hypothermia for 72 h except in the trial reported by Gunn et al\(^{22}\) where cooling was discontinued between 48 and 72 h if newborns recovered neurologically. Newborns with mild encephalopathy were excluded from the analysis.

**METHODOLOGICAL QUALITY OF THE INCLUDED STUDIES**

All the included studies used appropriate methodology following the Cochrane review guidelines.\(^{23}\) Assessment of the risk of bias among the included studies is reported in Table 3. Overall, the methodology of the 7 studies was strong, particularly in the 3 largest completed trials\(^{10,12,13}\) and the 2 trials that were stopped early due to the loss of clinical equipoise as assessed by independent data monitoring committees.\(^{20,22}\) Two trials had moderate methodological quality. The trial by Gunn et al\(^{22}\) was limited by a small sample size. It also had addi-
tional newborns randomized in other reports.28,30 The trial by Zhou et al22 may not be generalizable because of the higher proportion of males included (87% in the selective head-cooling group and 83% in the control group) and is weakened by high attrition (17% lost to follow-up). Also in the trial report by Zhou et al,22 the outcome of 5% of the subjects was assessed by pediatricians in local hospitals rather than by blinded-certified neurologists. In none of the trials were caregivers blinded to the treatment assignment. The study protocol was violated in 2 trials with the inclusion of 19% to 20% of newborns with mild HIE.20,22 The assessment of publication bias using funnel plots indicated no substantial evidence of publication bias in the primary outcome of death or severe disability in newborns with moderate or severe HIE (Figure 1).40 More details about the methodological quality of the included trials are reported in the eAppendix.

**PRIMARY OUTCOME: COMPOSITE OF DEATH OR MAJOR NEURODEVELOPMENTAL DISABILITY AT 18 MONTHS**

The primary outcome was assessed in all 7 trials included in this review, representing 1214 newborns (Table 1). Therapeutic hypothermia reduced the risk of the composite outcome of death or major neurodevelopmental disability at age 18 months (RR, 0.76; 95% CI, 0.69-0.84; and NNT, 7; 95% CI, 5-10; I²=0%; Figure 2).

**SECONDARY OUTCOMES**

Each component of the composite primary outcome was examined. Hypothermia reduced the risk of death at age 18 months (RR, 0.75; 95% CI, 0.63-0.88; NNT, 11; 95% CI, 7-26; I²=0%; Figure 3). Among newborns who survived to 18 months, those treated with hypothermia had significantly lower rates of major disability (RR, 0.68; 95% CI, 0.56-0.83; NNT, 8; 95% CI, 5-16; I²=12%; Figure 3), cerebral palsy (0.62; 0.49-0.78; 8; 6-16; 33%; Figure 3), developmental delay (0.66; 0.52-0.82; 8; 5-18; 25%; Figure 3), and blindness (0.56; 0.33-0.94; 23; 12-207; 0%; Figure 3). The rate of deafness was 3.7% in newborns treated with hypothermia and 5.8% in newborns treated with normothermia, suggesting a protective effect of hypothermia that was not statistically significant (RR, 0.64; 95% CI, 0.32-1.27; I²=0%; Figure 3). Therapeutic hypothermia increased survival with normal neurological function (RR, 1.63; 95% CI, 1.36-1.95; NNT, 7; 95% CI, 5-11; I²=0%; Figure 4). Hypothermia reduced the risk of death or major disability both in newborns with moderate HIE (RR, 0.67; 95% CI, 0.56-0.81; NNT, 6; 95% CI, 4-11; I²=0%; Figure 5) and in newborns with severe HIE (0.83; 0.74-0.92; 7; 5-16; 0%; Figure 5). The risk of mortality or major neurodevelopmental disability was reduced by both total body cooling (RR, 0.75; 95% CI, 0.66-0.85; NNT, 6; 95% CI, 4-11; Figure 6) and selective head cooling (0.77; 0.65-0.93; 7; 4-21; Figure 6) when compared with normothermia. Statistical heterogeneity by I² was not significant for any of the analyses, indicating homogeneity among the included studies.

**SENSITIVITY ANALYSES**

The trial conducted by Simbruner et al21 was terminated early due to ethical concerns regarding controls (normothermia group); 14% of the randomized subjects were not included in the final analysis of this trial. Therefore, sensitivity analysis was performed assuming an extreme scenario (all the newborns lost to follow-up in the hypothermia group were affected with the primary outcome and all the newborns lost to follow-up in the normothermia group were unaffected). In this extreme scenario, the evidence remained in favor of the hypothermia group (RR, 0.76; 95% CI, 0.59-0.99).

Due to the methodological concerns in the trial by Zhou et al22 discussed earlier, a sensitivity analysis excluding the data from this study was carried out. The conclusion did not change in that the combined rate of death or major disability was lower in the hypothermia group compared with the normothermia group (RR, 0.77; 95% CI, 0.70-0.86; NNT, 7; 95% CI, 5-12) (eFigure 2). The sensitivity of the results to the exclusion of this trial was also examined in the subgroup analysis in newborns with moderate (n=557) and severe HIE (n=480); the results remained significantly in favor of hypothermia in newborns with moderate HIE (RR, 0.70; 95% CI, 0.58-0.84; NNT, 6; 95% CI, 4-13) (eFigure 3) and in newborns with severe HIE (0.84; 0.75-0.94; 8; 5-21) (eFigure 4).

**COMMENT**

This updated systematic review of the randomized controlled trials conducted in newborns with HIE supports that therapeutic hypothermia is effective in reducing the risk of death or major disability at age 18 months in newborns with either moderate or severe HIE. An important outcome of this review is that hypothermia re-
duced the mortality rate without increasing the disability rate in asphyxiated newborns. This outcome was indicated by a decrease in the rate of major disability and an increase in the rate of survival with normal neurological function.

The homogeneity of the included studies (patient inclusion and exclusion criteria, study design, methodological quality, and length of follow-up) increases the confidence that therapeutic hypothermia improves the long-term outcomes at 18 months in different clinical settings.

Experimental and clinical evidence had previously suggested that outcomes after hypothermic treatment were strongly influenced by the severity of HIE, with less effective neuroprotection following severe HIE. Severe HIE is associated with a shorter latent phase (the period between reestablishment of apparently normal cerebral metabolism after HIE and the start of secondary energy failure and its irreversible neurotoxic cascade), worse secondary energy failures and more cortical-gray matter neuronal death. The extensive brain injury in severe HIE involving the basal ganglia and thalami are often associated with abnormalities in specific cortical and subcortical white matter. Moderate and severe lesions in the basal ganglia and thalami and severe white matter lesions are associated with cerebral palsy. Although the evidence from this review suggests that newborns with severe HIE will benefit, therapeutic hypothermia seems to be more beneficial to newborns with moderate HIE than newborns with severe HIE (relative risk reduction, 33% vs 17%). The diversity in the timing and magnitude of the brain injury in newborns with moderate and severe HIE may have led to a differential treatment effect.

Although hypothermia decreases rates of death or disability, newborns who are profoundly asphyxiated will not likely benefit from hypothermic therapy. Identifying newborns who are untreatable can be a challenge; therefore, early predictors of nonresponders are required to individualize treatment decision. Six moderately asphyxiated newborns or 7 severely asphyxiated newborns need to be treated to save 1 newborn from death or major disability.

Edwards et al in a recent meta-analysis estimated that the RR of composite outcome of death or major disability reached statistical significance in newborns with moderate HIE (RR, 0.73; 95% CI, 0.58-0.92) and did not reach statistical significance in newborns with severe HIE (RR, 0.87; 0.75-1.01). Based on their results, these authors recommended that "...clinicians make individual decisions on whether to treat newborns with severe encephalopathy." Their review did not include 3 recent trials. With the inclusion of these trials and the higher number of newborns available for analysis, it is clear that newborns with severe HIE also benefit from therapeutic hypothermia.
The assessment of the severity of encephalopathy is difficult, imprecise, and subjective when based on clinical evaluation alone. Two of the included trials that used clinical criteria alone violated their protocol and included newborns with mild HIE.42,43 Newborns with mild HIE were not expected to benefit from hypothermia.47 None of the adverse events of death or severe disability occurred in newborns with mild HIE in the trial reported by Zhou et al.22 However, in the trial by Jacobs et al.,33 33% and 25% of newborns with mild HIE in the control and cooled groups, respectively, died or had severe disability; the authors related the recruitment of newborns with mild HIE to the lack of a standardized neurological assessment tool to assess encephalopathy. One may speculate that newborns may be misclassified in regard to their degree of encephalopathy and subsequently receive suboptimal treatment decisions. The combination of the aEEG and the neurological examination shortly after birth enhances the ability to identify high-risk newborns and limits the number of newborns who would be falsely identified when they are assessed with either evaluation alone.88

The realistic therapeutic window of hypothermia is uncertain.1-13 Experimental evidence suggests that the neuroprotective response of hypothermia is influenced by the timing of initiation of therapy.50,51 In all included trials, the timing of initiation of hypothermia was no more than 6 hours after birth. Li et al.32 suggested that delaying the onset of therapy by 6 to 10 hours after birth did not negatively affect the rate of moderate to severe disability and
sensitivity analyses. The current analysis was able to re-
sample size, detailed subgroup analyses, and
the inclusion of recent trials, increased power based on
peutic hypothermia as soon after birth as possible for new-
the strengths of this updated systematic review are

dead when compared with newborns treated within 6 hours
after birth. The National Institute of Child Health and Hu-
man Development is evaluating late hypothermia for new-
borns with HIE initiated between 6 and 24 hours of age
(ClinicalTrials.gov Identifier: NCT00614744). Until fur-
ther evidence is available, it seems prudent to initiate thera-
peutic hypothermia as soon after birth as possible for new-
borns with moderate to severe HIE.

The strengths of this updated systematic review are
the inclusion of recent trials, increased power based on
increased sample size, detailed subgroup analyses, and
sensitivity analyses. The current analysis was able to re-

---

**Figure 5.** Forest plot of the primary outcome of death or major disability in survivors in newborns with moderate to severe hypoxic ischemic encephalopathy. Diamond indicates overall summary estimate for the analysis (width of the diamond represents the 95% CI). M-H indicates Mantel-Haenzel test.

---

**Figure 6.** Forest plot for the primary outcome of death or major disability by method of cooling in newborns with moderate to severe encephalopathy. Diamond indicates overall summary estimate for the analysis (width of the diamond represents the 95% CI). M-H indicates Mantel-Haenzel test.
fine the confidence with which clinicians should offer therapeutic hypothermia in newborns with moderate to severe HIE.

The unblinded nature of the included studies will remain the major limitation of the available evidence about therapeutic hypothermia. The current evidence is limited to 18-month follow-up data; therefore, it remains appropriate for clinicians to be conservative when counseling parents about longer-term neurological function. Long-term follow-up of the newborns in the trials reported to date will provide data to examine if neurological data recorded at 18 months accurately predict long-term neurological function. As the outcome of birth asphyxia is devastating, work should continue to find adjuvant therapy to hypothermia.

Accepted for Publication: December 7, 2011.

Correspondence: Mohamed A. Tagin, MB, BCh, The Hospital for Sick Children, 555 University Ave, Toronto, Ontario M5G 1X8, Canada (mohamed.tagin@utoronto.ca).

Author Contributions: Drs Tagin, Vincer, and Whyte had full access to all the data in this review and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Tagin. Acquisition of data: Tagin, Woolcott, Vincer, Whyte, and Stinson. Drafting of the manuscript: Tagin. Critical revision of the manuscript for important intellectual content: Tagin, Woolcott, Vincer, Whyte, and Stinson. Statistical analysis: Tagin. Study supervision: Whyte.

Financial Disclosure: None reported.

Online-Only Material: The eAppendix and eFigures are available at http://www.archpediatrics.com. This article is featured in the Archives Journal Club. Go to http://www.archpediatrics.com to download teaching PowerPoint slides. Visit http://www.archpediatrics.com to listen to an author podcast about this article.

REFERENCES


