Hypothermia for Perinatal Brain Hypoxia-Ischemia in Different Resource Settings: A Systematic Review

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Summary
Objective: To assess the effect of hypothermia on mortality of neonates with hypoxic-ischemic encephalopathy in different economic resource settings.
Methods: We searched for randomized controlled trials on MEDLINE, Embase and other databases. Duplicate reviewers selected the studies and extracted data. We calculated meta-analyses of the relative risks (RR) and 95% confidence intervals (95% CI), and used meta-regression to evaluate the gross domestic product per capita influence on hypothermia efficacy.
Results: Sixteen studies were included (n = 1889); eight were conducted in lower income countries (n = 662). Hypothermia significantly reduced mortality (RR = 0.77; 95% CI: 0.65–0.92). Meta-regression revealed that hypothermia efficacy does not increase as the gross domestic product per capita rises.
Conclusions: There is enough evidence to support hypothermia as the standard care for hypoxic-ischemic encephalopathy. Evidence from low-resource settings is limited, but hypothermia efficacy was not shown to be associated with better resource countries.

Key words: Induced hypothermia, newborn infant, brain hypoxia-ischemia, developing countries.

Introduction
Hypoxic-ischemic encephalopathy is a dramatic condition with a poor prognosis and high mortality rate, depending on the severity of the injury [1]. Survivors often exhibit chronic morbidity, such as cerebral palsy, mental retardation, learning disorders and other central nervous system injuries [2]. Systematic reviews of randomized controlled trials (RCTs) have shown evidence of the efficacy and safety of using hypothermia to prevent sequel and death due to hypoxic-ischemic encephalopathy [3–6]. Most RCTs were performed in high-income countries with a well-developed neonatal health care infrastructure to manage hypothermia. Little evidence exists to show that the use of this therapeutic modality is safe in less-equipped health care environments, such as those found in developing countries [7].

Our objective was to assess the more current evidence about hypothermia effect on the mortality of neonates with hypoxic-ischemic encephalopathy and whether this technique is effective in lower resource settings.

Methods
Protocol and registration
The current review was registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration number: CRD42012003496.

Eligibility criteria
We included RCTs that analyzed the influence of whole body hypothermia or selective head cooling on newborn mortality from hypoxic-ischemic encephalopathy compared with normothermia. We only included studies that fulfilled all criteria. There were no restrictions for language, length of follow-up, publication date or status.

Information sources
We searched MEDLINE, Embase, Scopus, ProQuest, Web of Science, Cochrane Central
Register of Controlled Trials (CENTRAL), metaRegister of Current Controlled Trials (mCRT), Latin American and Caribbean Center on Health Sciences Information (LILACS) and Scientific Electronic Library Online (SciELO). The last search was performed in April 2013. We also screened the references of relevant articles to identify potentially eligible studies.

**Search**

We used the following strategy for MEDLINE (via PubMed): (“perinatal”[tiab] or “newborn”[tiab] or “neonate”[tiab] or “infant”[tiab]) and (“cool”[tiab] or “cooling”[tiab] or “temperature”[tiab] or “temperature”[mesh] or “body temperature”[tiab] or “body temperature”[mesh] or “hypothermia”[tiab]) and (“hypoxic-ischemic”[tiab] or “hypoxic-ischemic”[tiab] or “hypoxic-ischemic”[tiab] or “asphyxia”[tiab] or “hypoxia”[tiab] or “brain”[tiab] or “encephalopathy”[tiab]) and (therapy/broad[filter]).

**Study selection and data collection process**

Three researchers (T.F.G., M.T.S., M.C.M.) independently reviewed the retrieved studies and elaborated a data extraction sheet to collect the data. One author extracted the data and the other two confirmed the extraction. Disagreements were resolved by authors’ consensus.

We extracted the following information from the articles: country, method of cooling, average cooling temperature, cooling duration, length of follow-up, severity of encephalopathy, each study’s inclusion and exclusion criteria and the number of deaths in the intervention and control groups.

**Risk of bias and quality assessment**

To assess the risk of bias in individual studies, we followed the Cochrane Collaboration tool [8] and RevMan 5.1 software. This toll rates as ‘low’, ‘unclear’ or ‘high’ risk of bias each of the following items: sequence generation, allocation sequence concealment, blinding, incomplete outcome data, selective outcome reporting and other potential sources of bias. All the studies were considered as having a low risk of bias due to blinding, once the absence of blinding would not interfere in the mortality assessment. Publication bias was assessed by analyzing funnel plot asymmetry and by Peters’ test [9] and Harbord’s test [10].

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the quality of the outcomes [11]. In this approach, five items that can decrease the quality of evidence were assessed: limitations (risk of bias), inconsistency, indirectness, imprecision and publication bias. The quality of evidence was rated as high, moderate, low or very low.

We considered the quality assessment results when interpreting the findings. We used GRADEpro 3.6 software to create an evidence profile table with the quality assessment results.

**Data analysis**

The primary outcome was the relative risk (RR) of death, following intention-to-treat analysis [8].

The meta-analyses of the RR were grouped by the random-effects Mantel–Haenszel model and presented with 95% confidence intervals (95% CI). We also performed a meta-regression by the logarithm of RR and gross domestic product (GDP) per capita, in purchasing power parity (PPP) for each country. In multicenter studies, we calculated the mean GDP [12]. All analyses were performed with STATA 10.1 software. Heterogeneity of the results was estimated by the $I^2$, Tau² and $\chi^2$ ($p > 0.10$) tests.

To perform the meta-analysis, we stratified studies by the method of cooling and the economy classification of the country where the study was conducted, based on the definitions from the World Bank List of Economies (low-income economies, lower-middle-income economies, upper-middle-income economies and high-income economies) [13]. In multicenter studies, the country of highest economic level was considered.

**Results**

Our literature search identified a 1255 unique records (Fig. 1). By screening titles and abstracts, we selected 25 records to be fully assessed from which we excluded three articles. The 22 remaining publications represented 16 individual studies.

**Study characteristics**

The 16 unique studies included 1889 patients [14–35]. Of those, 952 were randomized to the induced hypothermia group and 937 to the normothermia control...
group. There were 398 deaths, 175 in the hypothermia group and 223 in the control group. All the studies were published in English. Five studies were multicenter, but all countries were of the same income level—high-income economies. Eight studies were conducted in lower-income countries, with 662 patients (35%) in total [18, 23–25, 27, 33–35]. All studies performed in high-income and upper-middle-income countries used commercially acquired cooling devices (cooling blanket, cooling mattress or cooling cap), except for Jacobs 2011, in which they used refrigerated gel packs to induce hypothermia [30–32]. RCTs performed in low-middle income used refrigerated gel packs [34, 35], and the RCT performed in a low-income country—induced hypothermia with a cooling mattress made by water bottles filled with cold water from the tap [25]. Two studies did not detail how the systemic cooling was performed [24, 33]. Most studies included only children with moderate to severe encephalopathy and used Sarnat’s clinical staging system to assess the degree of encephalopathy [36]. Some studies used encephalographic findings to determine the degree of encephalopathy and one study [25] used the Thompson score [37] (Table 1). Supplementary Table 1 depicts the detailed inclusion criteria of the RCTs.

Risk of bias and quality of evidence
The risk of bias assessment is presented in Supplementary Table 2. Incomplete outcome data (attrition bias) and other bias were the items of higher risk of bias across studies.

The funnel plot revealed an asymmetry among the studies (Supplementary Fig. S1), but Peters’ test \( p = 0.50 \) and Harbord’s test \( p = 0.70 \) suggested that publication bias was not significant. \( \Gamma^2 \), Tau squared, and \( \chi^2 \) tests did not identify heterogeneity across the studies’ results.

Supplementary Table 3 presents the assessments of the quality of evidence of the primary outcome, death. The quality of evidence was high, as all items were judged as satisfactory.

Meta-analysis and meta-regression
Hypothermia significantly reduced the risk of death in neonates with hypoxic-ischemic encephalopathy when compared with normothermia (RR = 0.77; 95% CI: 0.65–0.92; \( \Gamma = 0% \)). When stratifying by method of cooling, only the studies that used whole body cooling studies showed efficacy (Fig. 2).

When the outcome data were stratified by country income, the results showed a reduction statistically significant in mortality due to hypothermia, in the studies performed in high (RR = 0.81; 95% CI: 0.67–0.97) and in upper-middle income economies (RR = 0.52; 95% CI: 0.28–0.95). Studies in lower-income countries usually had smaller sample sizes and lacked statistical power to assess the outcome, resulting in nonsignificant results (Supplementary Fig. S2).

The meta-regression did not show a statistically significant relation between the logarithmic RR and the GDP (in PPP) of the studies’ countries \( p = 0.58 \), and no residual variation due to heterogeneity was detected \( (\text{Tau}^2 = 0; \Gamma = 0\% \) ; Fig. 3).

Discussion
Our analysis showed that therapeutic hypothermia appears to be a safe and effective treatment to prevent mortality in infants with hypoxic-ischemic encephalopathy. Studies in lower income economies did not have statistic power to detect significant effects of hypothermia after stratification by country income, but the meta-regression failed to show that a country’s GDP per capita, an indirect measure of health care resources, affects the efficacy of hypothermia. From available data, hypothermia efficacy did not show to be related to better resources settings.

Limitations
Our review only considered mortality as the outcome, to allow a more detailed analysis for this critical outcome. Previous systematic reviews also considered other outcomes, such as physical disabilities and mental impairment, and found significant efficacy of hypothermia on these outcomes [3–5, 7, 40–42].

Because blinding was not possible, this may remotely influence cases were the baby was known to be part of the hypothermia group. In such cases, the family could ask to insist in the treatment, based on the hope of a positive outcome. In our study, we did not compare withdrawal rates across the studies; nevertheless, other review that assessed the differences in withdrawal rates did not find differences in this decision [5].

RCTs protocols followed strict inclusion criteria, not recruiting premature babies, for example. This kind of limitation is unrealistic in daily practice [43]. Ongoing studies are recruiting infants to fill this gap of knowledge [44, 45].

Lower resource settings
Several reasons may cause a difference between the results in low resource settings and developed countries [25, 46, 47], including complications of labor, maternal conditions, lack of trained personnel and adequate equipment for neonatal resuscitation. Also, a ‘natural cooling’ phenomenon may exist in the control group, where the spontaneous hypothermia that occurred after birth was not corrected by the local standard of care, and might have diluted the induced hypothermia effect [48].

The accessibility of cooling devices was not an obstacle to the implementation of the practice in lower resource settings. It was possible to induce
<table>
<thead>
<tr>
<th>Study</th>
<th>Country (income level [13])</th>
<th>Dates of enrolment</th>
<th>Method of cooling</th>
<th>Target temperature (°C)</th>
<th>Duration of cooling (hours)</th>
<th>Length of follow-up</th>
<th>Severity of encephalopathy (criteria adopted)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Battin 2001 [14–16]</td>
<td>New Zealand (high)</td>
<td>1996–98</td>
<td>Selective (cooling cap)</td>
<td>36.5–36.0; 35.9–35.5; 34.5–35.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>48–72</td>
<td>18 months</td>
<td>Mild to severe (Sarnat)</td>
<td></td>
</tr>
<tr>
<td>Shankaran 2002 [17]</td>
<td>USA (high)</td>
<td>1999–2000</td>
<td>Systemic (cooling blanket)</td>
<td>34.5</td>
<td>72</td>
<td>Until hospital discharge</td>
<td>Moderate to severe (own criteria)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Akisu 2003 [18]</td>
<td>Turkey (upper-middle)</td>
<td>2000–01</td>
<td>Selective (cooling cap)</td>
<td>33.5–33.0</td>
<td>72</td>
<td>Until hospital discharge</td>
<td>Mild to severe (Sarnat)</td>
<td></td>
</tr>
<tr>
<td>Shankaran 2005 [19, 20]</td>
<td>USA (high)</td>
<td>2000–03</td>
<td>Systemic (cooling blanket)</td>
<td>33.0–34.0</td>
<td>72</td>
<td>22 months</td>
<td>Moderate to severe (Sarnat)</td>
<td></td>
</tr>
<tr>
<td>Gluckman 2005 [21]</td>
<td>USA, New Zealand, UK (high)</td>
<td>1999–2002</td>
<td>Selective (cooling cap)</td>
<td>34.0–35.0</td>
<td>72</td>
<td>18 months</td>
<td>Moderate to severe (Sarnat)</td>
<td></td>
</tr>
<tr>
<td>Eicher 2005 [22]</td>
<td>USA, Canada (high)</td>
<td>1998–2001</td>
<td>Systemic (cooling blanket)</td>
<td>32.5–33.5</td>
<td>48</td>
<td>12 months</td>
<td>Mild to severe (Sarnat)</td>
<td></td>
</tr>
<tr>
<td>Lin 2006 [23]</td>
<td>China (upper-middle)</td>
<td>2000–03</td>
<td>Selective (cooling cap)</td>
<td>34.0–35.0</td>
<td>72</td>
<td>10 days</td>
<td>Mild to severe (Sarnat)</td>
<td></td>
</tr>
<tr>
<td>Bhat 2006 [24]</td>
<td>India (low-middle)</td>
<td>Not mentioned</td>
<td>Systemic (not specified)</td>
<td>33.5</td>
<td>72</td>
<td>Until hospital discharge</td>
<td>Severe (not mentioned)</td>
<td></td>
</tr>
<tr>
<td>Robertson 2008 [25]</td>
<td>Uganda (low)</td>
<td>2007–07</td>
<td>Systemic (cooling mattress made by bottles filled with cold water)</td>
<td>33.0–34.0</td>
<td>72</td>
<td>17 days</td>
<td>Mild to severe (Thompson)&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Azzopardi 2009 [26]</td>
<td>UK, Hungary, Sweden, Israel, Finland (high)</td>
<td>2002–06</td>
<td>Systemic (cooling blanket)</td>
<td>33.0–34.0</td>
<td>72</td>
<td>18 months</td>
<td>Moderate to severe (aEEG findings)</td>
<td></td>
</tr>
<tr>
<td>Zhou 2010 [27]</td>
<td>China (upper-middle)</td>
<td>2003–05</td>
<td>Selective (cooling cap)</td>
<td>33.8–34.2</td>
<td>72</td>
<td>18 months</td>
<td>Mild to severe (Sarnat)</td>
<td></td>
</tr>
<tr>
<td>Simbruner 2010 [28, 29]</td>
<td>Germany, Austria, France, Italy, Belgium, Denmark, Singapore (high)</td>
<td>2001–06</td>
<td>Systemic (cooling mattress)</td>
<td>33.5–34.0</td>
<td>72</td>
<td>21 months</td>
<td>Moderate to severe (aEEG findings)&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Jacobs 2011[30–32]</td>
<td>Australia, New Zealand, Canada, USA (high)</td>
<td>2001–07</td>
<td>Systemic (cold gel packs)</td>
<td>33.0–34.0</td>
<td>72</td>
<td>24 months</td>
<td>Mild to severe (Sarnat)</td>
<td></td>
</tr>
<tr>
<td>Thayyil 2011 [33]</td>
<td>India (low-middle)</td>
<td>Not mentioned</td>
<td>Systemic (not specified)</td>
<td>33.5</td>
<td>72</td>
<td>11 days</td>
<td>Mild to severe (not mentioned)</td>
<td></td>
</tr>
<tr>
<td>Bharadwaj 2012 [34]</td>
<td>India (low-middle)</td>
<td>2009–11</td>
<td>Systemic (cold gel packs)</td>
<td>33.0–34.0</td>
<td>72</td>
<td>6 months</td>
<td>Moderate to severe (Sarnat)</td>
<td></td>
</tr>
<tr>
<td>Joy 2012 [35]</td>
<td>India (low-middle)</td>
<td>2010–12</td>
<td>Systemic (cold gel packs)</td>
<td>33.0–34.0</td>
<td>72</td>
<td>Until hospital discharge</td>
<td>Moderate to severe (Sarnat)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Eeach group of six children was enrolled to one of the three temperature ranges.
<sup>b</sup>Estudy used own criteria to determine the severity of encephalopathy, which was similar to Sarnat score; however, it was not cited in the article.
<sup>c</sup>EThe study also assessed the Sarnat stage at the third day, but the initial grading of the encephalopathy was made by the Thompson score.
<sup>d</sup>EInformation available in other reports [38, 39].
Fig. 2. Effect of hypothermia on mortality, compared with control.

Fig. 3. Meta-regression of logarithm of the RR of death and the countries’ GDP per capita (in PPP).
hypothermia with less expensive devices, such as gel packs made of plastic containing gel materials used to store vaccines [34, 35].

In countries with fewer resources, many deliveries are performed by midwives, far from a health care center. Once there is a higher incidence of hypoxic-ischemic encephalopathy in these settings, it becomes necessary to find interventions that are feasible and effective in such scenarios, especially for prevention of hypoxic-ischemic encephalopathy. A Zambian study showed a significant reduction in the incidence of encephalopathy by training midwives and providing a kit for home deliveries [49].

Since the last systematic reviews published [6, 50], three RCTs conducted in developing countries were concluded and published [33–35]. Such results were also not considered in the last update of the Cochrane review [51]. Present review includes the most updated and complete data in the field.

Conclusion
Hypothermia prevents death in neonates with hypoxic-ischemic encephalopathy and should be the standard treatment for infants with this condition. Our findings indicate that hypothermia efficacy is not associated with the income level of the country, an indirect measure of the resources settings. More research is needed in developing economies to bring robust evidence about hypothermia efficacy in such areas.

Supplementary Data
Supplementary Data are available at Tropej article.

References


