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Original Article

Safety of Moderate Hypothermia for Perinatal Hypoxic-Ischemic Encephalopathy: A Meta-analysis

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ABSTRACT

BACKGROUND: We investigated the safety of therapeutic hypothermia during intervention in infants with hypoxic-ischemic encephalopathy (HIE). **METHODS:** The MEDLINE, EMBASE, PubMed, and the Cochrane Central Register of Controlled Trials from onset to November 30, 2016 were searched for studies on perinatal HIE. Randomized controlled trials comparing the use of therapeutic hypothermia with normothermia for perinatal HIE were included in the study. Safety and efficacy data for therapeutic hypothermia in 1806 infants with HIE were included in this meta-analysis. The primary outcomes were safety variables, and the secondary outcomes were efficacy variables. A fixed-effect model was used to perform the meta-analysis. Risk ratios (RR), risk differences (RD), and 95% confidence intervals (CI) were calculated. **RESULTS:** Thirteen trials, including 1806 infants, contained information on safety and efficacy variables. Moderate hypothermia significantly increased the risk of thrombocytopenia (RR 1.18, 95% CI 1.02 to 1.37, $P = 0.03$; RD 0.06, 95% CI −0.02 to 0.09) and cardiac arrhythmia (RR 2.52, 95% CI 1.62 to 3.93, $P < 0.0001$; RD 0.19, 95% CI 0.09 to 0.03) during intervention. **CONCLUSIONS:** In infants with HIE, the application of therapeutic hypothermia increases the risk of thrombocytopenia and cardiac arrhythmia during intervention.

Keywords: hypothermia, hypoxic-ischemic encephalopathy, infants, side effects

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Introduction

Perinatal hypoxic-ischemic encephalopathy (HIE) is a main cause of death and disability worldwide, despite advances in knowledge gained about HIE from *in vitro* and *in vivo* experiments. There is also no specific treatment for HIE.[1] Prolonged moderate hypothermia reduces cerebral injury and improves neurological outcome because irreversible neuronal damage after hypoxic-ischemic injury does not occur for several hours.[2] Several randomized controlled trials that investigated the application of therapeutic hypothermia during perinatal HIE have been conducted since 1998.[3-15] However, the results of these clinical trials are not conclusive, and few studies report adverse effects during intervention.[5-11,14] Although the studies provide point estimates that show a treatment benefit, it is uncertain whether application of therapeutic hypothermia is safe in infants with HIE.[4,6,8-10]

A 2010 meta-analysis in the *British Medical Journal* concluded that moderate hypothermia reduces death and neurological impairment due to HIE in infants assessed 18 months after treatment. However, the meta-analysis focused on neurological outcomes rather than on adverse effects.[16] In 2013, an updated Cochrane Library review evaluated some adverse effects; however, few conclusions were positive[17] except for a relative risk of thrombocytopenia (less than 150,000) in the therapeutic hypothermia group of 1.21 (95% confidence interval [CI] 1.05 to 1.40)

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Clinical Trial Registration: The study has not been registered due to the study design of meta-analysis.

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compared with the control group. In an earlier, smaller review, for thrombocytopenia (less than 100,000) the RR was 1.51 (95% CI 1.02 to 2.10).[18] We believe that their results were related to the small sample size for the included studies.

We performed a meta-analysis that includes new research and additional data that were recently made available from previously reported research. This previous research shows the potential for therapeutic hypothermia to increase the risk of adverse effects including thrombocytopenia and cardiac arrhythmia during intervention. Our meta-analysis determines the safety of therapeutic hypothermia during interventions in infants with HIE.

Materials and Methods

Search methods

Relevant studies were identified from Google Scholar, PubMed, MEDLINE (using the Mesh terms ["Infant, Newborn" AND "Asphyxia and Hypoxic Ischemic Encephalopathy"] and "Hypothermia"), EMBASE, and the Cochrane Central Register of Controlled Trials, and from previous reviews including abstracts, cross-references, conferences, expert informants, symposium proceedings, and manual journal searches. We updated this search in November, 2016, and did not include the additional unpublished data and unpublished studies. Studies were identified by members of our study group, and relevant studies were selected by consensus.

Selection criteria

We included all randomized controlled trials comparing the use of therapeutic hypothermia with standard care (normothermia) for perinatal HIE. The methodologic quality of the assessed studies was recommended by the Cochrane Collaboration neonatal review group, which relies on whether randomization and not being aware of the intervention were used, and based on completeness and unawareness of follow-up.[19]

The participants were required to meet the following criteria: (1) newborn infants 36 weeks' gestation or greater; (2) evidence of birth asphyxia, with each enrolled infant satisfying at least one of the following criteria: (i) Apgar score of 5 or less at ten minutes; (ii) mechanical ventilation or resuscitation at ten minutes; (iii) cord pH less than 7.1, or an arterial pH less than 7.1, or base deficit of 12 or more within 60 minutes of birth; and (3) evidence of encephalopathy according to Sarnat staging,[20,21] as follows: (i) stage 1 (mild): hyper-reflexia, hyper-alertness, dilated pupils, hypotonia with a weak suck, weak Moro reflex, and seizures; (ii) stage 2 (moderate): hyper-reflexia, lethargy, bradycardia, miosis, hypotonia with weak suck, and seizures; (iii) stage 3

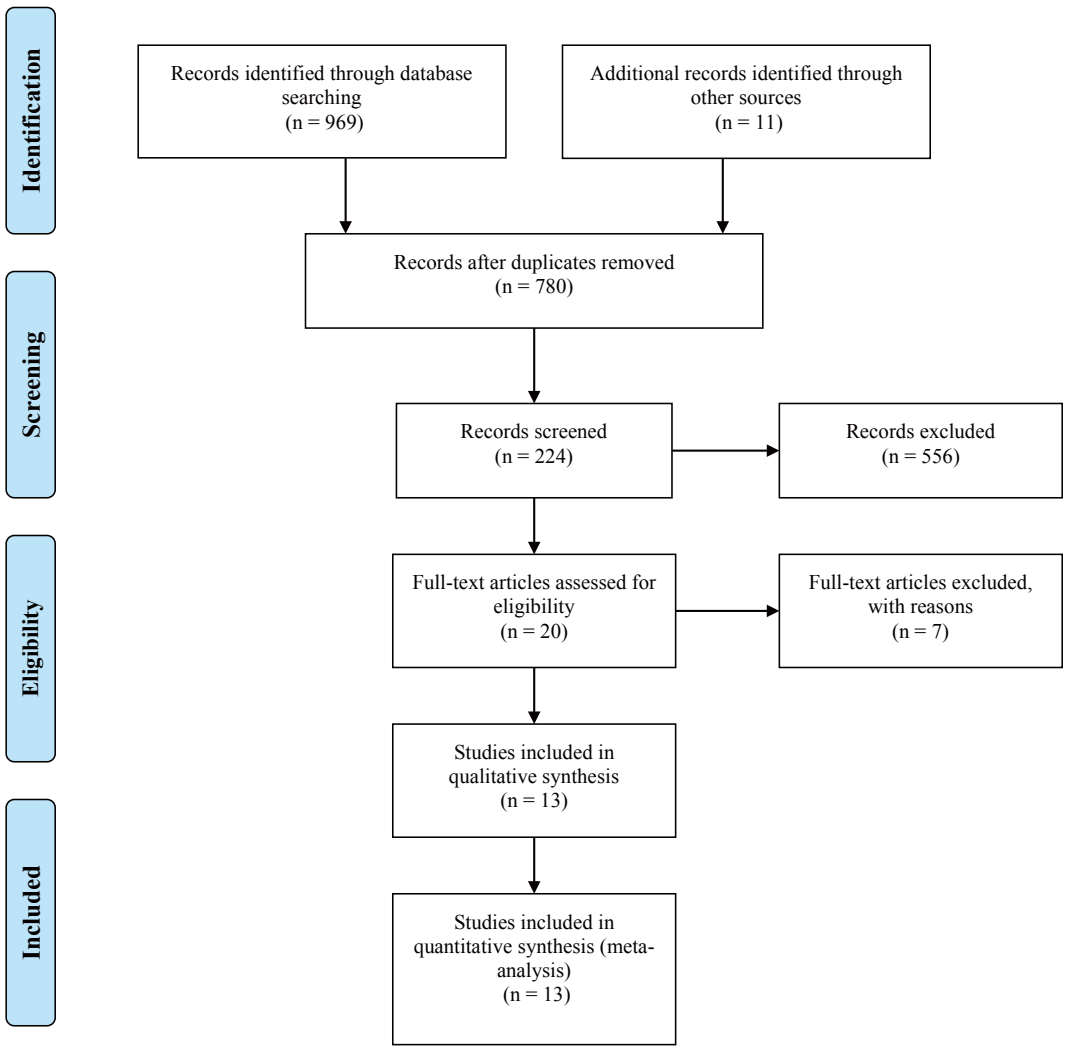

FIGURE 1.
Study selection. (The color version of this figure is available in the online edition.)