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Therapeutic Hypothermia for Neonatal Encephalopathy in Low- and Middle-Income Countries: A Systematic Review and Meta-Analysis

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ABSTRACT

Therapeutic cooling represents the main treatment strategy for neonatal hypoxic-ischemic encephalopathy in developed countries, although its efficacy and safety in low- and middle-income countries remain unclear. The present meta-analysis aims to gather the available evidence in the field and assess whether therapeutic hypothermia is able to reduce mortality in neonates from low- and middle-income countries. The effects in other clinical outcomes, such as disability, sepsis, thrombocytopenia and hemorrhage will be also evaluated. The credibility of evidence will be appraised using the GRADE approach.

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1 Background Hypoxic-ischemic encephalopathy (HIE) a major cause of mortality and long-term morbidity in neonates. The condition is much more common in low- and middle-income countries compared to high-income ones. Therapeutic cooling represents an important tool for HIE management. However, a recent large-scale randomized controlled trial, in contrary to available literature, did not show the benefit of therapeutic hypothermia in neonates with HIE from developing countries.

2 Eligibility criteria The population of the study will consist of neonates with gestational age ≥34 weeks and birthweight ≥1800 g diagnosed with hypoxic-ischemic encephalopathy, diagnosed and staged with the Sarnat criteria. The intervention of interest is therapeutic hypothermia (selective head or whole body) initiated within the first 6 hours of life. The control group should be treated with standard care. The primary outcome of interest is mortality till the end of the

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follow-up period. Secondary outcomes include the composite of death or severe disability (evaluated at the age of ≥6 months), as well as sepsis, shock, acute kidney injury, thrombocytopenia, clinically significant hemorrhage, major cardiac arrhythmia and length of hospital stay. Only randomized controlled trials or quasi-randomized trials conducted in low- and middle-income countries will be included. Observational studies, conference abstracts, review articles and in vitro studies will be excluded.

3 Information sources PubMed, Scopus, Web of Science, CENTRAL (Cochrane Central Register of Controlled Trials) and Clinicaltrials.gov will be searched from inception. Google Scholar should provide grey literature coverage. No date/language restrictions will be applied.

4 Data extraction Extracted data will be the following: year of publication, country, eligibility criteria, type of cooling, device and cost, core temperature target, timing of hypothermia, number of patients, patients' gender, mean gestational age, birthweight, 5-minute Apgar score, percentage of cesarean deliveries, proportion of neonates with severe HIE and inborn neonates.

5 Quality assessment The risk of bias will be assessed with the RoB-2 tool, which evaluates the following domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported results. The credibility of outcomes will be appraised with the GRADE approach.

6 Data analysis Random-effects models will be fitted to provide estimates of risk ratio (RR) for binary outcomes or mean difference (MD) for continuous outcomes. Heterogeneity will be measured with the inconsistency index. The 95% predictive intervals will be calculated as an estimate of the effects to be expected in future studies in the field. Subgroup analyses are planned based on country, year of publication, sample size, type of hypothermia and cost of the cooling device. Sensitivity analysis will be performed by the separate analysis of studies at public hospitals and of those including only inborn neonates. Funnel plot asymmetry will be assessed with the Egger's test. As an additional analysis, one-stage meta-analysis will be conducted.

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