Considering the use of induced hypothermia in a pediatric patient with traumatic brain injury: A critical appraisal of two meta-analyses

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Objective: **To review whether induced hypothermia after traumatic brain injury affects morbidity and mortality based on the results of two meta-analyses.**

Design: **Critical appraisals of McIntyre et al: Prolonged therapeutic hypothermia after traumatic brain injury in adults: A systematic review. *JAMA* 2003; 289:2992–2999, and Henderson et al: Hypothermia in the management of traumatic brain injury: A systematic review and meta-analysis. *Intensive Care Med* 2003; 29:1637–1644.**

Findings: **Both meta-analyses included trials of adult patients with severe traumatic brain injury randomized to induced hypothermia or normothermia and evaluated risk of death and poor neurologic outcomes. McIntyre et al. found the overall relative risk of mortality with induced hypothermia to be 0.81 (95% confidence interval 0.69–0.96). By designing *a priori* analyses, these authors also found that the relative risk of death was reduced in patients cooled for >48 hrs, and the risk of poor neurologic outcome was reduced with all durations of cooling, cooling to 32–33°C, and rewarming in <24 hrs. In contrast, Henderson et al. found that induced hypothermia did not change the odds of death after traumatic brain injury (odds ratio 0.81; 95% confidence interval 0.59–1.13) and that normothermic controls had an odds ratio of 0.42 (95% confidence interval 0.25–0.70) for developing intercurrent pneumonia. Both analyses found trials to be heterogeneous with respect to neurologic outcome.**

Conclusions: **The discrepancies in the results of these contemporaneous meta-analyses may stem, in part, from differences in their trial selection strategies as well as from sources of trial heterogeneity. Nevertheless, McIntyre et al. uncovered the equivalent of a dose-dependent reduction in the risk of death with induced hypothermia, supporting further study of this neuroprotective strategy. Although these meta-analyses included trials containing adult patients, a phase II trial of induced hypothermia in pediatric traumatic brain injury has established its feasibility and safety in infants and children. As in adult patients, induced hypothermia for traumatic brain injury in children can be considered an optional therapy for refractory intracranial hypertension but should not be regarded as standard of care. (Pediatr Crit Care Med 2006; 7:468–472)**

CLINICAL SCENARIO

A 9-yr-old girl falls while climbing a tree. She awakens confused when she is discovered by her parents. She is somnolent but arousable, and her Glasgow Coma Scale score is 11 at her initial emergency room assessment. Just before computed tomography of her head, her Glasgow Coma Scale deteriorates to 5. She is intubated, and as she has sustained no other injuries, she is treated empirically for intracranial hypertension and brought to the intensive care unit after her scan. She does not have a skull fracture, but there is an intraparenchymal hemorrhage with edema of the right hemisphere. An intraventricular monitoring device is placed, and your team tailors therapy to reduce intracranial pressure and optimize cerebral perfusion pressure in accordance with the Guidelines for the Medical Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents (1).

The girl's parents wonder whether induced hypothermia might help their daughter, as they saw a talk show testimonial about an adult who had been "saved from brain damage" after a cardiac arrest with hypothermia. You remember that induced hypothermia is thought to target many aspects of the pathophysiology of brain injury in general (2) and has been shown to be beneficial after types of hypoxic-ischemic injury (3–6). You and the team search PubMed using the strategy "hypothermia" AND "traumatic brain injury," limiting the results to "meta-analyses" since no clear recommendations have been put forward despite several large trials in the

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Table 1. Comparisons of meta-analyses by McIntyre et al. (9) and Henderson et al. (10)

	McIntyre et al. (2003)	Henderson et al. (2003)
Are the results valid?		
Specific clinical question addressed?	Yes	Yes
Trial search comprehensive?	Yes	No, non-English trials and unpublished RCTs excluded
All included trials of high methodological quality?	No, but trial quality did not affect results	No, and effect on results not assessed
Publication bias assessed?	Yes, no bias found	No
Assessments of trials reproducible?	Yes	Yes
What are the results?		
Were the trials homogeneous?	For mortality—yes For poor outcome—no	For mortality—yes For mortality + poor outcome—no
No. of trials	12	8
No. of patients	Hypothermia: 543 Normothermia: 526	Hypothermia: 379 Normothermia: 368
Did hypothermia decrease mortality?	Yes; RR, 0.81 (95% CI, 0.69–0.96)	No; OR, 0.81 (95% CI, 0.59–1.13)
Did hypothermia decrease poor neurologic outcome?	Studies not combinable RR, 0.78 (95% CI, 0.63–0.98)	Studies not combinable OR, 0.75 (95% CI, 0.56–1.01)
Did hypothermia affect rate of pneumonia?	Not assessed	Yes; normothermic patients had lower rate OR, 0.42 (95% CI, 0.26–0.70)

RCTs, randomized, controlled trials; RR, relative risk; CI, confidence interval, OR, odds ratio.

past 10 yrs. You remind your team that meta-analyses (or systematic reviews) pool patient results from several randomized, controlled trials (RCTs) to approximate a true treatment effect. Your search recovers two meta-analyses, both published in 2003, that studied the impact of induced hypothermia after traumatic brain injury (TBI) in adults. Unfortunately, only two small RCTs have been performed in children to date. You also find that the meta-analyses included many of the same trials. Their abstracts, however, suggest that the study conclusions are contradictory.

You update the family that a quick review of the literature reveals little information pertinent to children, but you promise to get back to them after becoming more informed. You set out to critically review both meta-analyses, approaching them using a format recommended by accepted evidenced-based medicine guides (7, 8). As part of your review, you compare and contrast the analyses to determine any differences between them (Table 1).

CRITICAL APPRAISAL OF MCINTYRE ET AL. AND HENDERSON ET AL.

Did the Overviews Address a Focused Clinical Question? Yes, both analyses sought to determine whether induced hypothermia alters mortality and neurologic outcome after TBI in adults. Both analyses defined poor neurologic outcome as a Glasgow Outcome Score consistent with severe disability, vegetative state, or death. Additionally, McIntyre et al. (9) sought to determine *a priori* if the depth and duration of hypothermia as well as rate of rewarming influenced these end points, whereas Henderson et al. (10) sought to determine whether induced hypothermia increased the risk of pneumonia.

Were the Criteria Used to Select Articles for Inclusion Appropriate? In general, both analyses used appropriate criteria. However, differences in the respective criteria led to differences in which trials were included and differences in outcome measures. In the analysis by McIntyre et al., inclusion criteria specified study design (RCT), target population (adults with TBI), therapeutic intervention, and comparison (≥24 hrs of therapeutic hypothermia at any time after sustaining TBI vs. normothermia), as well as primary and secondary outcomes (all-cause mortality and neurologic outcome). Whereas Henderson et al. also included RCTs that used induced hypothermia after TBI and examined at least one clinically relevant outcome, the authors did not specify a population (although all studies that met their criteria enrolled adults only). Henderson et al. further limited their trials to those that were published and in English only.

Is It Unlikely That Important, Relevant Studies Were Missed? It is unlikely that McIntyre et al. missed relevant trials. MEDLINE was electronically searched without language restriction, using appropriate MeSH terms and text words. Additional searches were also performed using supplemental databases, published RCTs, and subject reviews. Authors of RCTs were queried for unpublished studies, abstracts, and ongoing trials. In contrast, by limiting their search to English-language journals and published RCTs, Henderson et al. missed several studies. Thus, in the Henderson analysis there were eight studies reviewed whereas in the McIntyre there were 12, two of which were published in Chinese journals. In addition, authors of RCTs were not queried for ongoing or unpublished trials, potentially further limiting their findings.

Were the Primary Studies of High Methodological Quality? Both meta-analyses were limited in this respect. McIntyre et al. appraised the included trials according to whether the trials concealed randomization until patients were enrolled and whether adjudicators were blinded to neurologic outcome. They stratified methodological quality into "high" (allocation concealed, outcome blinded), "moderate" (allocation concealment unclear, outcome blinded), and "low" (allocation concealment unclear, outcome not blinded.) Of 12 included trials, two were of high grade, three of moderate grade, and five of low grade; two trials were not assigned a grade because they did not assess neurologic outcome. Henderson et al. provided the reader with a less objective strategy for assessing trial quality. Although it is possible to give

more weight to studies of higher methodological quality when performing a meta-analysis, these meta-analyses did not employ such weighting. McIntyre et al. performed sensitivity analyses to explore whether the methodological quality of the trials altered their results, and no such effect was observed. Sensitivity analysis was not performed by Henderson et al.

Publication bias refers to the greater likelihood of studies to be published that demonstrate a positive treatment effect. Thus, inclusion of only published data in a meta-analysis increases the risk of overestimating a treatment effect. Publication bias was reportedly absent in the McIntyre analysis and was not evaluated in the analysis by Henderson.

Were Assessments of Studies Reproducible? In both analyses, more than one reviewer agreed on the trials to be included. Only in the McIntyre analysis was appraisal of trial quality also assessed by more than one reviewer.

Were the Results Similar From Study to Study? In other words, within each meta-analysis, were the results of each trial sufficiently similar that they could be combined to make a single estimate applicable across populations, interventions, and outcomes? In the McIntyre analysis, relative risks (RRs) of mortality fell in favor of hypothermia in six of 12 trials, in favor of normothermia in one trial, and nearly on the line of no difference in five trials. All estimates of RR were close to unity, and the 95% confidence intervals (CIs) for all trials overlapped significantly. In the Henderson analysis, results were tabulated as odds ratios (ORs, e.g., odds of dying in the hypothermia groups vs. odds of dying in the control groups). Of eight included trials, odds ratios ranged from 0.19 to 1.44, and again 95% CIs overlapped.

Both analyses employed formal tests of heterogeneity. With respect to mortality, the trials in both analyses were statistically homogeneous; that is, the trials in each meta-analysis were sufficiently similar to be combined. However, McIntyre et al. also considered, *a priori*, the possibility that differences in depths and durations of hypothermia achieved among the trials and their periods of rewarming may affect results and so analyzed these specifically. With respect to poor neurologic outcome, the trial data included in both analyses were statistically heterogeneous and thus were not combinable. Hence, summary statistics should not have been derived from them.

What Are the Overall Results of the Review? Overall results are summarized in Table 1. In the McIntyre analysis on 12 RCTs (totaling 1,069 patients), the pooled RR of death was 0.81 (95% CI, 0.69–0.96). This 19% reduction in the risk of death remained even if the largest trial was removed from the analysis. In subgroup analyses planned *a priori*, RR of death was reduced further in patients cooled for >48 hrs (0.79; 95% CI, 0.57–0.91). Neither the depth of cooling (33.5–34.5 vs. 32–33°C) nor the length of rewarming (≤24 hrs vs. >24 hrs) had an effect on the relative risk of death. Although trial quality reportedly did not influence pooled risk of death, the highest quality studies had RRs slightly greater than 1 whereas studies of moderate or poor quality had RRs of 0.2–1.0. In the Henderson analysis of eight RCTs (totaling 748 patients), the pooled OR for mortality in the hypothermic group was 0.81 (95% CI, 0.59–1.13; $p = .22$), demonstrating an insignificant benefit from hypothermia.

Although the trials in both analyses were heterogeneous with respect to neurologic outcome, McIntyre et al. reported an RR of poor neurologic outcomes of 0.78 (95% CI, 0.63–0.98). In subgroup analyses, the RR was lower if patients were cooled for 24 hrs or >48 hrs, with cooling to 32–33°C, or with rewarming in <24 hrs. Henderson et al. also reported an odds of death or poor neurologic outcome favoring the hypothermia group (OR, 0.75; 95% CI, 0.56–1.01; $p = .06$), although the results were not statistically significant and the trials were not combinable in this respect.

Henderson et al. also evaluated the effect of hypothermia on the development of pneumonia. Five of eight trials reported pneumonia rates. Although no testing for heterogeneity was performed on this data, the pooled OR for pneumonia in the normothermic group was 0.42 (95% CI, 0.25–0.70; $p = .001$); that is, the controls had a statistically lower rate of pneumonia.

RESOLVING THE DISCREPANCIES

Trial Selection. Because meta-analyses consolidate and analyze data from existing RCTs to approximate a true treatment effect, results depend fundamentally on the trial identification and inclusion process. The inclusion of additional trials in the McIntyre analysis affected the reported combined risk of death. McIntyre et al. did not limit their searches to the English language, allowing them to discover two additional RCTs published in Chinese journals. They also included two other trials that were excluded by Henderson et al., which were of either low or unknown methodological quality.

Tangible and Intangible Sources of Heterogeneity. Homogeneity among included trials is the second most important determinant of the validity of meta-analysis results—trials must be adequately homogeneous clinically, methodologically, and statistically if data from them are to be combined. Authors routinely test for homogeneity with respect to the outcomes under consideration such as mortality and neurologic outcome. Unfortunately, when studies are *not* homogeneous, authors are still inclined to calculate a treatment effect and report the result while disclosing that the studies were found to not be combinable. This is the case with both meta-analyses here—studies were *not* homogeneous with respect to neurologic outcome, and yet a treatment effect was reported ("beneficial" in McIntyre et al.'s analysis; nonstatistically so in Henderson et al.'s). As the appropriateness of this practice is questionable, readers should accept results regarding neurologic outcomes in the appraised meta-analyses with appropriate caution, or not at all.

Other underlying differences among the trials of each meta-analysis may also have confounded results. For example, McIntyre et al. identified that the time to initiation of cooling was unclear in four of their 12 studies. Included trials did not report comorbid illnesses. Henderson et al. discussed that the three trials that showed the greatest treatment effects did not address how temperature was managed in the control groups—that is, whether hyperthermic patients were actively cooled or hypothermic patients were actively warmed. Thus, if fever in control patients was not appropriately managed, these trials may have demonstrated a "deleterious effect of hyperthermia rather than a beneficial effect of hypothermia" (10). The uniformity of intracranial pressure (ICP) management strategies across trials (such as use of neuromuscular blockade and sedation, osmotic agents, diuretics, barbiturates, fluid therapy, and vasoactive agents) was difficult to discern in trials of both anal-

yses. Trials varied with respect to the time points at which they reported outcomes (3 months, 6 months, 1 yr, or all of these). Trials also did not mention how frequently target temperatures were achieved. Such intangible sources of heterogeneity may unpredictably influence meta-analysis results.

Both meta-analyses may have chosen to report heterogeneity more quantitatively in the form of I^2 or τ^2 values. These easily calculated statistics go beyond simply relating the *p* value for heterogeneity testing; they estimate what percentage of the inherent variability among trials is due to true heterogeneity vs. chance, thus conveying how much heterogeneity affects the final summary result (11).

DO THE RESULTS HELP US IN CARING FOR OUR PATIENT?

Were All Clinically Important Outcomes Considered? Both McIntyre et al. and Henderson et al. considered mortality and neurologic outcome (severe vs. mild-to-moderate), which are the most important outcomes to consider after severe TBI. More subtle neurologic sequelae such as learning disabilities and behavioral and emotional disorders are worthy considerations in milder head injuries, especially in children (12–14)), and were not assessed in these reviews.

Additionally, Henderson et al. examined rates of pneumonia in hypothermia vs. control groups and found a significant association of pneumonia with hypothermia. This is useful information and has been previously described (15). In fact, children with submersion injury who present hypothermic may have sustained neutropenia (16), implying a potentially greater susceptibility to infection in hypothermic states. Other known complications of hypothermia (cardiac arrhythmias, coagulopathy) are generally not seen at the depths of hypothermia achieved in these trials.

As the authors acknowledge, the impact of certain variables such as comorbid illnesses cannot be appreciated from these analyses. It is also important to note that patients were excluded from all trials if they had sustained multiple traumatic injuries.

Are the Benefits Worth the Harms and Costs? Clinical benefit is intuitively expressed in terms of "numbers needed to treat (NNT)." Unfortunately, an NNT cannot always be derived by simply pooling event rates from the trials of a meta-analysis (17, 18). Using an on-line calculator designed for NNT determination from meta-analyses (19) and a pooled control event rate to reflect baseline risk, we found from McIntyre's analysis that 16 patients treated with systemic hypothermia would prevent one death (95% CI, 10–73). Although the confidence interval is broad, this NNT is quite good when compared with other accepted interventions in medicine. For example, 210 adults following myocardial infarction need to be treated with angiotensin-converting enzyme inhibitors to prevent one death (20). On the other hand, the meta-analysis of Henderson et al. led them to conclude that utilization of induced hypothermia is not significantly beneficial after TBI. These authors also found an increased rate of pneumonia associated with the treatment.

Given the uncertainties that are inherent in meta-analyses, and the fact that a number of variables need to be validated in future RCTs (time to initiation of hypothermia, co-interventions with respect to ICP management, effects on comorbid illnesses and injuries, influence of patient age, and others), McIntyre et al. point out that "our results should not influence clinical practice at this time." Given that they find no benefit from induced hypothermia, and that pneumonia is an iatrogenic "cost" of treatment, Henderson et al. would likely agree.

Can the Results Be Applied to My Patient Care? The results of these meta-analyses cannot be directly applied to pediatric patients, as none of the included trials were performed in children. The developing brain is known to differ from adults in its susceptibility to traumatic injury (21–23). Accordingly, the developing brain may also be distinct in its response to hypothermia. In infants and children, hypothermia could be neuroprotective, but it could also cause harm. Thus, well-designed RCTs are necessary before the use of induced hypothermia after pediatric TBI is accepted as a standard of care.

Recent data give us cause for optimism that therapies helpful in adults will also be helpful in children. Two well-designed and executed RCTs have demonstrated that therapeutic hypothermia improves outcomes in adults after cardiac arrest (3, 4). Two recent RCTs in neonates have also demonstrated improved outcomes with therapeutic hypothermia after severe neonatal hypoxic-ischemic injury (5, 6), although one did so only in a subgroup with less severe electroencephalographic abnormalities (6).

Two RCTs that used induced hypothermia after TBI in children warrant discussion. Biswas et al. (24) randomized 21 pediatric patients to either receive induced hypothermia or be kept normothermic in addition to standard ICP management. This trial failed to demonstrate an improvement in ICP control with hypothermia, although a trend toward lower ICPs was observed in the hypothermia group. This RCT was published within the search window of both meta-analyses reviewed here; whereas McIntyre et al. limited their analysis to adult patients, Henderson et al. did not, and it is unclear why the trial by Biswas et al. was not included.

Adelson et al. (25) recently published a phase II multiple-center, randomized trial of induced hypothermia after severe pediatric TBI. In this trial of 75 children, hypothermia was used in a manner consistent with McIntyre et al.'s recommendations: target temperatures of 32–33°C were achieved in 13.8 ± 7.2 hrs, hypothermia was maintained for 48 hrs, and patients were rewarmed in 12–18 hrs. This study's primary importance was in demonstrating that the treatment regimen was feasible using surface cooling alone. Second, there were no differences in rates of infection, coagulopathy, and arrhythmia between treatment arms; arrhythmias seen in children treated with hypothermia were largely sinus tachycardia and were treatable with rewarming and volume resuscitation. Third, children treated with hypothermia had significantly better controlled ICPs within the first 24 hrs and had a tendency to have lower ICPs during the 5-day study period (although rebound intracranial hypertension was observed in some). Finally, outcomes favored reduced mortality and better neurocognitive recovery by 6 months. Currently, a phase III trial is underway in children to study the effects of induced hypothermia in traumatic brain injury (26).

The findings of McIntyre et al. also suggest that perhaps we are still learning the best way to use induced hypothermia after TBI. Induced hypothermia appears to have a narrow therapeutic time window, and excessive time lapse from brain injury to induction of hypothermia is cited as an important reason why clinical trials have failed to show an effect (27). By designing subgroup analyses *a priori*, McIntyre et al. were able to discern that

deeper cooling (32–33°C) of longer duration (>48 hrs) and with rapid rewarming (<24 hrs) is likely to improve outcomes most significantly after TBI. This observation is the equivalent of a "dose" effect and, in itself, supports further study of induced hypothermia after TBI as a neuroprotective strategy.

SCENARIO RESOLUTION

You revisit the family after having carefully reviewed these articles and other relevant literature. You inform them that two reviews of trials looking at hypothermia after TBI in adults have reached mixed conclusions about its benefit. Furthermore, there are only two small trials in children demonstrating the feasibility of using induced hypothermia after TBI. Thus, although induced hypothermia may be considered an option for the management of refractory intracranial hypertension at experienced centers (1), it is premature at this time to regard this therapy as standard of care for either children or adults. You also inform them that you are continuing with therapies that are recommended by the currently accepted guidelines (1). Your patient has moderate elevations in ICP during the next 72 hrs, but these resolve with the recommended interventions. Within a week she is extubated and is developing appropriate arousal, although she has weakness and slurred speech. She is discharged to a rehabilitation facility 2 wks later.

Your patient and her family visit your intensive care unit in 6 months. Her speech has cleared and her motor deficits are nearly resolved, although her parents state she is having some difficulty with schoolwork and impulse control. You are surprised to learn that she is the star pitcher on her Little League team.

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