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Role of therapeutic hypothermia in improving outcome after traumatic brain injury: a systematic review

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Editor's key points

- This review aims to address an important issue of primary therapeutic hypothermia in traumatic brain injury.
- Overall 18 randomized controlled trials, involving 1851 patients, were identified.
- Hypothermia was associated with cerebrovascular disturbances on rewarming, and possibly increased incidence of pneumonia.
- No benefit on mortality or neurological morbidity could be identified from high quality trials.

Summary. This systematic review delineates the effect of primary therapeutic hypothermia (PTH) (initiated on presentation of the patient) on both mortality and neurological outcome in patients with traumatic brain injury. The safety profile of the therapy is also assessed. A systematic search of the following databases was performed: MEDLINE, EMBASE, Zetoc database of conference proceedings, the Cochrane Database of Systematic Reviews, and the clinicaltrials.gov website, up to July 28, 2011. Relevant journals were hand-searched for further articles and reference lists were checked against the retrieved results for additional resources. The retrieved results were filtered for randomized controlled trials in English where systemic hypothermia was applied for ≥12 h in the treatment arm and outcome was assessed at a minimum of 3 months. Randomized controlled trials were assessed for quality of evidence using the GRADE system. Eighteen randomized controlled trials (1851 patients) were identified. The overall relative risk of mortality with PTH when compared with controls was 0.84 [95% confidence interval (CI)=0.72–0.98] and of poor neurological outcome was 0.81 (95% CI=0.73–0.89). However, when only high-quality trials were analysed, the relative risks were 1.28 (95% CI=0.89–1.83) and 1.07 (95% CI=0.92–1.24), respectively. Hypothermia was associated with cerebrovascular disturbances on rewarming and possibly with pneumonia in adult patients. Given the quality of the data currently available, no benefit of PTH on mortality or neurological morbidity could be identified. The therapy should therefore only be used within the confines of well-designed clinical trials.

Keywords: brain injuries; hypothermia, induced; morbidity, critical care; mortality

Traumatic brain injury (TBI) is a major cause of death and disability throughout the world. Each year in the European Union, TBI accounts for 1 000 000 hospital admissions, for the majority of the 50 000 road traffic deaths, and for more than 10 000 severely neurologically impaired survivors.[1] The mortality and long-term morbidity of the disease are therefore associated with a huge financial and societal burden. Strategies to improve outcome therefore have a pivotal role in the acute management of patients with TBI.

The concept that therapeutic hypothermia may prove to be one such strategy evolved after the discovery that the final neuronal injury pattern after an ischaemic insult to the brain could be manipulated by variations in brain temperature.[2] Subsequent animal models of TBI have elucidated multiple pathways involved in neuronal injury which can be manipulated through the use of therapeutic hypothermia to positive effect (Fig. S1 in Supplementary Material online). As such, there is much clinical interest in the therapy and several clinical trials have now been conducted, leading the Brain Trauma Foundation to issue a level III recommendation for the use of primary therapeutic hypothermia (PTH) in the management of TBI in 2007.[3] Given the inconclusive nature of the data, the studies omitted from that meta-analysis, and the advent of further high-quality studies, this systematic review was undertaken to review the evidence now available and to re-evaluate the risks and benefits of PTH when used in the management of TBI. It aims to answer the following specific questions:

(i) Does PTH improve survival in patients with TBI?
(ii) Does PTH improve subsequent neurological function in patients who survive TBI?
(iii) Is PTH safe when used in the context of TBI?

PTH may be defined as the deliberate lowering of core body temperature initiated on presentation of the patient, in order to achieve a beneficial outcome. This should be differentiated from therapeutic hypothermia initiated reactively in response to a change in the patient's clinical state, usually an increase in intracranial pressure (ICP).

Methods

A systematic search of the MEDLINE and EMBASE databases was conducted with medical librarian assistance from 1966 to July 28, 2011, using the search terms 'traumatic brain injury', 'traumatic brain injury hypothermia', and 'hypothermia intracranial pressure'. Filters were applied for clinical trials and review articles. Additional searches were performed using the search term: 'hypothermia, induced [Mesh] and brain injuries [Mesh]' and 'induced hypothermia [Emtree] and traumatic brain injury [Emtree]'. A search of the Zetoc database of conference proceedings was performed using the search term 'hypothermia traumatic brain injury'. The Cochrane Database of Systematic Reviews was searched using the terms 'traumatic brain injury', 'traumatic brain injury hypothermia', and 'hypothermia intracranial pressure'. A search of the clinicaltrials.gov website was performed using the search term 'traumatic brain injury hypothermia'. Executive researchers of relevant trials were contacted via e-mail for further information on their respective studies. Relevant journals were hand-searched for further references. The abstracts of the retrieved results were analysed for relevance and appropriate papers were obtained in full for further analysis. Reference lists from selected articles and from review articles were then checked against the retrieved results for additional resources.

The following *a priori* minimum inclusion criteria were then applied to the articles obtained:

(i) English language.
(ii) Randomized controlled trial in patients with TBI.
(iii) Use of induced systemic hypothermia for $\geq$12 h in the treatment arm.
(iv) Assessment of survival and neurological outcome at a minimum of 3 months after injury.

The articles selected were assessed for quality of evidence by each author independently using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system of assessment.[4 5]

Relevant data were extracted from each paper by hand and entered into a spreadsheet (Excel, Microsoft Corporation, Redmond, WA, USA). These data included: details of trial design facilitating assessment of quality, number of patients, injury details (injury severity score, Glasgow coma score, ICP, and the nature of the brain injury, differences in baseline covariates), cooling details (site of temperature measurement, target temperature in study and control groups, time to achieving target temperature, method of cooling, whether active warming was used in the control group, trigger for rewarming, rate of rewarming, presence of pyrexia in the control arm), use of barbiturates, complications (cardiovascular, neurological, infectious, haematological), and outcomes (neurological morbidity and mortality). The power of each study and the relative risk of mortality and neurological outcome with respective confidence intervals were calculated if they were not presented in the paper. The assessment of neurological outcome was based on the dichotomized Glasgow outcome score (GOS) in adults and on the dichotomized paediatric cerebral performance category (PCPC) in children (Tables S2 and S3, Supplementary Material online); this was calculated from raw data where necessary. A GOS of 1–3 or a PCPC of 3–6 was used to indicate a poor neurological outcome. Forest and funnel plots were performed to facilitate data consolidation (RevMan 5.1, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). The outcome from both fixed and random effects models were obtained in the meta-analysis; the model used did not influence the ultimate outcome and so the fixed effect model is presented in the Results section on the assumption that the same treatment effect was being assessed. The impact of duration of cooling and duration of follow-up on neurological morbidity and mortality was examined, along with the effect of confounding variables such as the effect of cooling on ICP.

Results

The results of the literature search are illustrated in Figure 1. Eighteen randomized controlled trials were selected and are summarized in Table 1. The authors independently reached consensus as to the quality of each trial. The overall quality of the evidence was graded as low. Fifteen trials were conducted in adults and three in children; three trials were graded as high quality, two as moderate, six as low, and seven as very low.

Does therapeutic hypothermia reduce mortality post-TBI?

A forest plot examining the pooled effect of PTH on mortality is shown in Figure 2. The relative risk of mortality after PTH compared with normothermia in TBI is 0.84 [95% confidence interval (CI)=0.72–0.98]. A funnel plot suggests that publication bias among this data set is unlikely (Fig. 3).

Only the trials by Clifton and colleagues,[6] Hutchison and colleagues,[7] and Clifton and colleagues[8] were deemed to be of high quality and important variables of these trials are further summarized in Table 2. The two former trials were performed in adults; the latter in children. Neither found benefit of PTH in reducing mortality after TBI; indeed, there was increased mortality in the PTH group in the trial by Hutchison and colleagues. A forest plot of only high-quality trials yields a pooled relative risk of mortality of PTH compared with normothermia of 1.28 (95% CI=0.89–1.83) as shown in Figure 4.

Does therapeutic hypothermia improve neurological outcome post-TBI?

A forest plot examining the pooled effect of PTH on poor neurological outcome is shown in Figure 5. The overall relative risk of a poor neurological outcome with PTH compared with normothermia in TBI is 0.81 (95% CI=0.73–0.89). Significant heterogeneity is noted in the data. A funnel plot suggests that publication bias among this data set is unlikely (Fig. 6).