**Meta-analysis of therapeutic hypothermia for traumatic brain injury in adult and paediatric patients**

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**ABSTRACT**

**Objective**: Therapeutic hypothermia has been used to attenuate the effects of traumatic brain injuries (TBI). However, the required degree of hypothermia, length of its use and its timing are uncertain. We undertook a comprehensive meta-analysis to quantify benefits of hypothermia therapy for TBI in adults and children by analysing mortality rates, neurological outcomes and adverse effects.

**Data Sources:** Electronic databases PubMed, Google Scholar, Web of Science, Cochrane Central Register of Controlled Trials and [ClinicalTrials.gov](http://ClinicalTrials.gov) and manual searches of studies were conducted for relevant publications up until February 2016.

**Study Selection:** 42 studies of adults (n = 3109, age range 18-81 years) and 8 studies in children (n = 454, age range 3 months-18 years) met eligibility criteria.

**Data Extraction:** Baseline patient characteristics, enrollment time, methodology of cooling, target temperature, duration of hypothermia and rewarming protocols were extracted.

**Data Synthesis:** Risk Ratios (RR) with 95% confidence intervals (CI) were calculated. Compared with adults who were kept normothermic, those who underwent therapeutic hypothermia were associated with 18% reduction in mortality (RR 0.82; 95% CI: 0.70-0.96; P = 0.01) and a 35% improvement in neurological outcome (RR 1.35; 95% CI: 1.18-1.54; P <0.00001). The optimal management strategy for adult patients included cooling patients to a minimum of 33℃ for 72 hours, followed by spontaneous, natural rewarming. In contrast, adverse outcomes were observed in children who underwent hypothermic treatment with a 66% increase in mortality (RR 1.66; 95% CI: 1.06-2.59; P = 0.03) and a marginal deterioration of neurological outcome (RR 0.90; 95% CI 0.80-1.01; P = 0.06).

**Conclusions:** Therapeutic hypothermia is likely a beneficial treatment following TBI in adults but cannot be recommended in children.

**Introduction**

The World Health Organisation predicts that by 2020 traumatic brain injury (TBI) will exceed many diseases as a major cause of death and disability (1) while the US Centers for Disease Control and Prevention estimates that 1.7 million Americans sustain a TBI every year, of which an estimated 52,000 die (2). European incidence is approximately 235 per 100,000 people with an average mortality rate of 15 per 100,000 (3).Epidemiology data for the prevalence of TBI within Asian populations is lacking (1), but estimates from India suggest that annually approximately 1.6 million individuals will sustain a TBI (4), while TBI is the leading cause of traumatic injury in China with approximately 10% of patients succumbing to death (5).

It is estimated that 5.3 million people in the USA (6) and 7.7 million people in the European Union (7) are living with a TBI-related disability. These disabled survivors are often unable to return to employment or school, with one study finding 50% of severely injured patients and 20% of patients with mild injuries failing to return to work one year post TBI (8). Studies from USA have estimated that $56.3 billion of expenditures occurs annually as a result of TBI from lost earnings of the patients and their carers (1).

Therapeutic hypothermia, a procedure in which the purposeful and controlled lowering of body temperature is performed, acts as a neuroprotectant to minimise neuronal loss or damage, with an aim to improve patient outcome (9). Therapeutic hypothermia can be divided into different levels according to the temperature achieved; mild (33-36°C) and moderate (28-32°C) are commonly used, while deep (10-28°C), profound (5-10°C), and ultra-profound (0-5°C) exist, but are rarely used (10). In the case of TBI, numerous animal experimental trials have produced positive results (11) but translating results to human studies with reliable guidelines has proved more challenging (12).

We aimed to conduct a comprehensive, systematic meta-analysis to robustly quantify the benefits of hypothermia therapy for TBI in adult and paediatric patients by analysing mortality rates, neurological outcomes and adverse effects.

**Materials and Methods**

**Study Identification**

Electronic databases PubMed, Google Scholar, Web of Science, Cochrane Central Register of Controlled Trials and [ClinicalTrials.gov](http://ClinicalTrials.gov) were searched for relevant published studies between 1940 and February 2016. Search (MeSH) terms “hypothermia”, “therapeutic hypothermia”, “cooling”, “induced hypothermia”, “brain injury”, “traumatic brain injury”, “head injury” and “head trauma” with the Boolean operators “AND” and “OR”. All languages were included and relevant papers were translated where necessary. Manual searching of the bibliographies of electronically identified studies was conducted.

**Study Selection Criteria**

Eligibility for TBI (including only blunt trauma) was based on the following inclusion criteria: (1) induced hypothermia rather than patients who were hypothermic upon admission, and; (2) Glasgow Outcome Scale (GOS) and/or mortality data allowing number of patients with favourable and unfavourable outcomes to be extracted. The control participants were not subject to temperature management except for fever control. Where duplicate studies were found to include the same patients cohorts in multiple trials, data from the most recent trial was used. Extra-cerebral trauma was excluded. PRISMA statement was used for reporting of this meta-analysis (13).

**Data Extraction**

Baseline characteristics of patients including age, sex, initial GCS (Glasgow Coma Scale), ethnicity, outcome data for GOS, mortality and frequency of pneumonia and cardiac arrhythmias was extracted. TBI was defined as mild (GCS 13-15), moderate (GCS 9-12) and severe (GCS 3-8). The duration of follow-up assessments to obtain outcome measures was documented. GOS data was dichotomised into favourable (score 4-5) and unfavourable (score 1-3) neurological outcomes. Mean GOS with standard deviations (SD) were extracted for use in a continuous outcome analysis quantifying the effectiveness of therapeutic hypothermia. Details of hypothermia induction and maintenance were extracted including patient enrollment time, methodology of cooling, target temperature, duration of hypothermia and rewarming protocols. Intracranial pressure and cerebral perfusion pressure goals and interventions to achieve these goals were also extracted.

Outcomes were divided into two categories: (1) safety of therapeutic hypothermia through recording of frequency events such as mortality, pneumonia and arrhythmias, and; (2) effectiveness of therapeutic hypothermia as a neuroprotectant to improve neurological outcome based on GOS. Analyses were conducted to examine the effects on the safety and effectiveness of therapeutic hypothermia of several parameters, such as: varying target temperatures, durations of maintained hypothermia, method of induced hypothermia, the rate at which patients were rewarmed. The influence of age and type of trial (randomised controlled vs observational) on the safety and effectiveness of therapeutic hypothermia were assessed. Target temperatures from some original studies were given as ranges: “mild” if the lowest temperature in the range was ≥33℃ or “moderate” if the lowest temperature in the range was <33℃.

**Statistical Analysis**

Pooled risk ratios were calculated with 95% confidence intervals (CI) by random effect model for analyses using dichotomous outcomes. Mean difference was calculated with 95% CI for continuous data outcomes. Funnel plots were constructed to assess publication bias. Statistical analysis was performed using Review Manager version 5.3.

**Patient Involvement**

Patients were not directly involved in this study as it is a meta-analysis.

**Results**

**Study Characteristics**

Of 1523 records identified, 49 studies (28 RCTs, 21 observational) met eligibility criteria (Fig 1) (14-62). In total, 3848 patients (73.4% male) were included (1922 therapeutic hypothermia group (TH); 1926 normothermic control group). The majority (41 studies) used adult patients with 43 studies using patients with a GCS ≤7 (Supplementary Table).

**Adult studies**

**Effect of Therapeutic Hypothermia on Favourable Neurological Outcome**

A significant 35% increase in favourable outcomes was seen in adults when patients were treated with therapeutic hypothermia (35 studies; 1561 TH; 1548 controls; RR 1.35; 95% CI 1.18-1.54; P < 0.00001). Moreover, this beneficial effect in adults was maintained in long-term (up to 24 months) (31, 34, 37, 41, 42) follow-up (208 TH; 192 controls; RR 1.64; 95% CI 1.33-1.55; P < 0.00001).

To ascertain a quantitative result for the level of neurological improvement seen in adults, a mean difference analysis was conducted to compare differences in mean GOS scores. GOS scores are significantly improved by 0.58 points for adults (24 studies; 985 TH; 955 controls; MD 0.58; 95% CI 0.30-0.87; P < 0.0001).

**Effect of Therapeutic Hypothermia on Mortality**

A significant reduction in mortality rates was seen with adult patients treated with therapeutic hypothermia (39 studies; 1710 TH; 1716 controls) with 18% decrease in deaths (RR 0.82; 95% CI 0.70-0.96; P = 0.01). Heterogeneity was observed within adult studies (I2 49%; χ 2 72.53; P = 0.0004) which was eliminated by excluding three studies (15, 29, 49) following which outcome results remained significant (RR 0.77; 95% CI 0.67-0.88; P = 0.0001). There was no suggestion of publication bias with symmetrical funnel plots.

**Effect of Methodological Assessment**

Analyses were conducted to assess any difference in outcome between RCTs and observational studies. Adult patients in both RCTs (RR 1.27; 95% CI 1.06-1.54; P = 0.01) and observational studies (RR 1.46; 95% CI 1.26-1.68; P < 0.00001) showed significantly improved neurological outcome when treated with therapeutic hypothermia. Similarly, overall mortality rates were reduced when patients were treated with therapeutic hypothermia with a significant effect from observational studies (RR 0.75; 95% CI 0.57-0.99; P = 0.04) and a strong trend from RCT data (RR 0.84; 95% CI 0.70-1.02; P = 0.07). By excluding one study (15) heterogeneity was eliminated and significant decreases in mortality rates in the RCT subgroup was obtained (RR 0.79; 95% CI 0.67-0.94; P = 0.008).

**Effect of Hypothermia Management**

Analyses were carried out to determine the best management strategy for hypothermia treatment. Aspects of management strategy considered were whether hypothermia was induced only in the head region or systemically; depth and duration of hypothermia; speed of rewarming, and; whether any adjunct interventions were used to control intracranial pressure.

The optimal management strategy to improve both morbidity and mortality was determined to be selective brain cooling to 33℃, maintaining this for 72 hours, followed by a period of spontaneous rewarming at the natural rate (Tables 1 & 2). The use of adjunctive therapy in addition to hypothermia, eg barbiturates, to reduce ICP limited the effectiveness of hypothermia (Tables 1 & 2). Those analyses with only a few included studies may exaggerate the effect size and therefore this must be treated with a degree of caution.

**Complication Rates**

Secondary complications to therapeutic hypothermia included pneumonia (17 studies; 527 TH; 432 controls) and cardiac arrhythmias (9 studies; 210 TH; 188 controls).

Patients undergoing hypothermia treatment were 28% more likely to suffer pneumonia compared to normothermic controls (RR 1.28; 95% CI 1.01-1.62; P = 0.04) but there was no significant increase in cardiac arrhythmias (RR 1.23; 95% CI 0.72-2.10; P = 0.46).

**Paediatric studies**

There was a significant 66% increase in mortality rate in paediatric studies (8 studies; 244 TH; 248 controls; RR 1.06; 95% CI 1.06-2.59; P = 0.03) (Fig 3). A 10% decrease in favourable neurological outcomes were seen in paediatric patients (6 studies; 225 TH; 229 controls; RR 0.90; 95% CI 0.80-1.01; P = 0.06) (Fig 2). GOS scores decreased by 0.17 points in children (3 studies; 67 TH; 64 controls; MD -0.17; 95% CI -0.64-0.31; P = 0.50).

**Discussion**

Therapeutic hypothermia is associated with significantly improved neurological outcome and reduced mortality rates in adult patients but is detrimental in children. This effect was most significantly seen in observational studies and the beneficial trend was also supported by RCTs, although its use in patients with a GCS above 13 is doubtful. The use of hypothermia as a therapy was not without risk. Hypothermic adults were more likely to get pneumonia, although cardiac arrhythmias were not more significantly seen.

The finding that treating adult patients with hypothermia significantly effects both neurological outcome and mortality rates in positive manners supports the conclusions drawn from one previous meta-analysis (63) but conflicts two more recent meta-analyses on the subject that showed the effects were non-significant (64, 65). Previous meta-analyses of studies focusing on paediatric patients found similar conclusions about the detrimental effects of therapeutic hypothermia for TBI patients with significant increases of 73% and 84% in the risk of mortality of children which correlate with the risk of 87% found in this study (66, 67).

Therapeutic hypothermia attenuates some of the secondary injury mechanisms that are initiated by a TBI. Studies on animals have shown that metabolism and cerebral blood flow are decreased by 5-7% for each degree Celsius that body temperature is decreased, therefore reducing oxygen consumption and carbon dioxide production (68, 69). Reducing oxygen consumption decreases the need for anaerobic metabolism which results in decrease of membrane permeability. This reduction in the influx of ions will reduce the cascade initiated by Ca2+ and Na+. It has also been shown that mild post-traumatic hypothermia reduced levels of excitatory neurotransmitters (70, 71), proinflammatory cytokines (72, 73) and lactate accumulation (74) in experimental studies. In addition to its ability to attenuate the events that lead to cellular apoptosis and necrosis, therapeutic hypothermia has also been shown to prevent apoptosis by reducing the levels caspase 3 and cytochrome C (mediators of apoptosis) (75).

Therapeutic hypothermia used for the purposes of neuroprotection has been established in areas of medicine other than for TBI, most notably for neonatal hypoxic encephalopathy (76, 77). Therapeutic hypothermia is being explored in further areas of medicine such as cardiac arrest, stroke and neurosurgery (78-80), but consensus as to whether the treatment is beneficial has not yet been reached.

Cooling patients to mild (above 33℃) or moderate (below 33℃) degrees of hypothermia produced very similar improvements in neurological outcome. However, mortality rate was reduced by 18% more with mild hypothermia compared to moderate hypothermia, suggesting that reducing body temperature by ~4℃ is required to elicit the beneficial effects of this treatment, which would correspond to a 20-28% decrease in cerebral metabolism and oxygen consumption. Hypothermia induced through selective head cooling using cooling caps and irrigation of the head with cold solution produced better patient outcomes compared to systemic cooling, but the number of studies in this group were small (28, 34).

Elevated ICP has been found to correlate with worsened outcome in TBI patients (81), possibly because of decreases in cerebral perfusion pressure and cerebral blood flow potentially leading to hypoxic-ischaemic injury (82). Hypothermia has long been known to reduce ICP therefore maintaining the treatment for a duration of 72 hours encompasses the start of the 3-10 day period in which intracranial hypertension secondary to the TBI may present, allowing early attenuation of the elevated ICP, preventing further brain damage. Our findings show that hypothermia for 72 hours appears to be the optimal duration, yielding the largest increase in favourable neurological outcome. Therapeutic hypothermia reduces ICP, as do barbiturates. Studies have shown that the additional use of barbiturates with therapeutic hypothermia did not improve neurological outcome or decrease mortality, compared to highly significant improvements by hypothermia alone. These results suggest that barbiturate therapy may limit the effectiveness of therapeutic hypothermia (44, 45).

The 72 hours of cooling should be followed by a period of natural rewarming where patients are allowed to spontaneously return to normal body temperature. The rewarming phase of hypothermia treatments has previously been associated with fatal rebounds in ICP, when lower ICP levels induced by cooling suddenly increase when cooling is removed due to temperature being increased too quickly (83). Allowing patients to rewarm passively at the natural rate may help avoid rapid changes in temperature, but not be too slow to prolong hypothermia for much longer than the optimum (83).

Due to their different physiology and metabolism to adults, children may have a very different response to injury (55) which may explain their unfavourable results. Following TBI, children have 70% of normal energy expenditure levels (84) compared to a hypermetabolic response in adults (85-87). Hypothermia acts to reduce metabolic response (88), therefore as children exhibit ~50% lower energy levels there may be less of a target for hypothermia to act upon, so outcomes cannot be improved. Another possible factor in this explanation comes from the fact that all 8 paediatric trials used barbiturates to control elevated ICP. Administration of barbiturates decreased metabolism to 14% below predicted levels compared to patients without barbiturate therapy who exhibited 26% above predicted levels (89). This mechanism would maintain low energy expenditure levels and reduce the target for hypothermia to act upon.

A number of limitations to our work need to be discussed. Variations in inclusion criteria to enroll patients could have affected our results and may account for some of the observed heterogeneity. However, much of this heterogeneity was eliminated by iterative analysis without affecting the significance of the results. One common inclusion criteria was that the TBI was a blunt injury; therefore it would be unwise to extrapolate these results for the use of therapeutic hypothermia in the treatment of penetrating trauma. More than half of the studies did not report any data for complications making it difficult to determine the full extent to which these arise. 37 studies reported that temperature was not actively maintained in the normal range within the normothermic control group. Therefore, in these studies the effect size may have been altered due to the deleterious effect of fever in the normothermic group, rather than the beneficial effects of cooling patients in the hypothermia group. GOS scoring to determine neurological outcome is cautioned as it uses short, unspecific descriptions. Finally, as with all meta-analysis there is a possibility of publication bias. However, we have attempted to undertake a comprehensive search and funnel plots were symmetrical but of course publication bias cannot be entirely excluded.

**Conclusions**

Therapeutic hypothermia is a likely beneficial treatment following TBI in adults, improving both neurological outcomes and decreasing mortality rates. Our work suggests that the optimal management strategy to improve both morbidity and mortality was determined to be selective brain cooling to 33℃. We then suggest maintaining this temperature for 72 hours, followed by a period of spontaneous rewarming at the natural rate, although the dataset for this advice is smaller. . Barbiturates may be used to control ICP but this may limit the effectiveness of the hypothermia therapy. Therapeutic hypothermia is not recommended for use in children with TBI. Randomized controlled trials with these targets in mind may help to provide more definitive clinical protocols.

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**Figure 1:** Flow chart illustrating steps in study identification and assessment of eligibility for inclusion in the meta-analysis. n = number of studies.

**Figure 2:** Risk ratio of favourable neurological outcome in hypothermia treatment group vs normothermia group for adult and paediatric studies.

**Figure 3:** Relative risk of mortality in hypothermia treatment group vs normothermia group for adult and paediatric studies.

**Table 1:** Relative benefit of hypothermia vs normothermia patients for favourable neurological outcome within subgroup analyses of adult patients.

**Table 2:** Relative risk of mortality for hypothermia vs normothermia patients within subgroup analyses of adult patients.