

Therapeutic hypothermia to reduce intracranial pressure after traumatic brain injury: the Eurotherm3235 RCT

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Scientific summary

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Background

Traumatic brain injury (TBI) is damage to the brain caused by trauma from incidents such as falls, traffic accidents and assault. It is a major cause of death and severe disability throughout the world and leads to around 1 million hospital admissions each year throughout the European Union (EU). TBI causes the majority of the 50,000 deaths from road traffic accidents and leaves 10,000 patients severely disabled each year; three-quarters of these victims are young people. This has a devastating emotional and physical impact and presents an enormous financial burden.

One of the most harmful consequences of TBI is cell injury and cell death in the brain. When this occurs, it starts a complex sequence of harmful, and potentially irreversible, processes at the cellular level. These processes can cause swelling (oedema) in the brain. This swelling increases the pressure inside the head and makes the injury worse. Preventing cell injury and death is therefore an important part of treatment. Cell death can occur from minutes to hours after injury and the harmful effects can last for 72 hours or longer. Thus, there may be a window of opportunity of several hours, or even days, during which cell death can be prevented by treatments such as hypothermia. Hypothermia treatment lowers the patient's temperature to below normal, which has a potentially beneficial effect on a number of problems caused by injury to brain cells.

In total, 29 studies in patients have been performed to assess the effects of hypothermia after TBI. These were of varying size and quality, but all observed reduced brain swelling and pressure levels inside the skull during hypothermia treatment. Thirteen of these studies reported significant improvements in patient outcome, with fewer deaths and less disability associated with hypothermia treatment.

Six major reviews of hypothermia studies were published between 2000 and 2008. Each review included differing numbers of trials, with varying quality of randomisation and blinding procedures. All six reviews found a trend towards positive effects of hypothermia on patient outcome, although only two reviews could statistically prove this. The most recent review included eight trials that enrolled comparable patient groups at entry to the trial (baseline). Hypothermia was found to reduce mortality by 20%, although this was not statistically proven. Further analysis showed that this effect was greatest when hypothermia was maintained for > 48 hours. Hypothermia was also associated with a trend towards improvement in patient outcome when measured by the Glasgow Outcome Scale (GOS) at 6 months.

A criticism of these reviews is that most failed to take account of important differences in patient groups (such as those with or without a build-up of pressure due to brain swelling) and differences in treatment protocols, except the use of hypothermia. Only two assessed whether or not the length of hypothermia treatment and speed of rewarming the body afterwards made a difference to the effectiveness of hypothermia. Results suggested that hypothermia treatment lasting for > 48 hours and rewarming rates of 24 hours, or 1 °C over 4 hours, may be factors that are important in reducing deaths and improving disability. However, the studies included in the review did not enrol enough patients to prove this.

In summary, the evidence from previous research shows that hypothermia treatment may be an effective therapy to improve outcome in patients who have suffered a TBI. Many trials have been carried out in this patient group, but none has been extensive enough to prove whether or not hypothermia is effective in preventing further brain damage and reducing death and disability. The Eurotherm3235 Trial aimed to provide a clear answer to this question.

Objectives

- Does therapeutic hypothermia (TH) (32–35 °C) improve patient outcome and reduce mortality 6 months after TBI as assessed by the Glasgow Outcome Scale – Extended (GOSE) questionnaire?

Secondary research questions:

- Does TH (32–35 °C) reduce intracranial hypertension?
- Is TH a cost-effective treatment to improve patient outcome after TBI?

Design

The Eurotherm3235 Trial was a pragmatic, multicentre randomised controlled trial (RCT) to examine the effects of hypothermia (32–35 °C) on patient outcome after TBI. The study recruited for 41 months.

Randomisation

Participants were randomised as soon as possible after meeting the inclusion criteria. The randomisation of participants to receive standard care with the addition of induced TH or standard care alone was undertaken using a central internet-based randomisation service.

Treatment allocation was minimised using the following baseline covariates:

- trial centre
- aged < 45 years or ≥ 45 years
- post-resuscitation Glasgow Coma Scale (GCS) motor component score of 1 or 2 or 3–6
- time from injury < 12 hours or ≥ 12 hours
- pupils – both reacting or one or neither reacting.

Participants allocated to the standard-care group received usual care without TH. Participants randomised to the intervention group received usual care with the addition of TH. Hypothermia was initiated with 20–30 ml/kg of refrigerated 0.9% saline given intravenously and maintained using the cooling technique available at each centre.

The depth of hypothermia (32–35 °C) was guided by intracranial pressure (ICP), with a higher pressure level warranting a cooler target temperature. TH of 32–35 °C was maintained for at least 48 hours and continued for as long as was necessary to reduce and maintain ICP at < 20 mmHg.

Blinded outcome assessment

The primary end point was patient outcome 6 months after TBI, assessed using the GOSE questionnaire. It was not possible to blind local investigators to allocation as it was clinically obvious which participants were receiving hypothermia because of, for example, the equipment required, participant temperature, blood results and fluid requirements. A blinded researcher therefore carried out participant outcome data assessment.

Setting

Induced hypothermia is a specialist intervention; therefore, only neurological ICUs that were familiar with the use of hypothermia treatment in this patient group were included. A total of 61 specialist neurological ICUs were opened as recruiting centres across 18 countries between 2009 and 2015: Belgium ($n = 8$), England ($n = 21$), Estonia ($n = 1$), Germany ($n = 1$), Greece ($n = 6$), Hungary ($n = 1$), India ($n = 3$), Ireland ($n = 1$), Italy ($n = 5$), Northern Ireland ($n = 1$), the Netherlands ($n = 1$), Portugal ($n = 1$), Russia ($n = 1$), Saudi Arabia ($n = 1$), Scotland ($n = 3$), Spain ($n = 4$), Abu Dhabi ($n = 1$) and Wales ($n = 1$).

Participants

Patients were assessed for eligibility to enter the trial on admission to the ICU by the health-care team. They continued to be screened for up to 10 days after the brain injury. If consent was given by the nearest relative/welfare guardian on the patient's behalf, the patient could enter the study and be randomised if/as soon as he or she met the inclusion criteria.

Interventions

Participants who were allocated to the hypothermia treatment group continued to receive their usual care along with having their temperature lowered to between 32 and 35 °C. The depth of cooling was guided by the severity of brain swelling, with more severe brain swelling warranting a lower temperature.

The participant's temperature was lowered in two stages.

Stage 1: induction of hypothermia

Participants were given 20–30 ml/kg of refrigerated 0.9% saline by a drip over 20–30 minutes. This quickly reduced their temperature to around 35 °C.

Stage 2: maintenance of hypothermia

After induction of hypothermia, the participant's temperature had to remain between 32 and 35 °C for at least 48 hours. Temperature could be maintained by using a variety of methods including placing ice packs under the arms and legs or using a special cooling machine. Each study centre used the available method of cooling as this was the most practical way to run the trial in many centres.

Participants were closely monitored for any signs of shivering throughout this period and any observed shivering was treated quickly. We provided a detection and management of shivering guideline to each recruiting centre.

Rewarming phase

No maximum duration of cooling was specified, although the doctor in charge of patient care was asked to consider rewarming the patient after 48 hours of hypothermia treatment. Rewarming was considered if the patient's ICP was stable and < 20 mmHg. Previous studies found that cooling for 48 hours and rewarming within 24 hours reduced deaths and disability in survivors.

Participants allocated to the hypothermia group were rewarmed at a rate of 0.25 °C per hour (1 °C per 4 hours); hence, all participants were rewarmed to normal temperature levels (> 36 °C) within 24 hours.

Treatment escalation

Occasionally, patients who have suffered a brain injury have severe brain swelling that does not respond to the usual treatment methods. These patients often require further treatment with other drugs or, sometimes, surgery. A proportion of participants in the Eurotherm3235 Trial did develop severe brain swelling and required further treatment.

Main outcome measures

The primary outcome was:

- patient outcome at 6 months after TBI, assessed using the GOSE questionnaire.

The secondary outcomes were:

- 6-month mortality rate
- intracranial pressure control
- incidence of pneumonia across both groups
- length of stay in the ICU and hospital
- Modified Oxford Handicap Scale (MOHS) score at 1 month, discharge from the randomising hospital or death, whichever took place first
- correlation between the predicted patient outcome using the MOHS score at hospital discharge and the predicted patient outcome using the GOSE score at 6 months post injury.

Results

We enrolled 387 patients at 47 centres in 18 countries (195 assigned to TH and 192 assigned to standard care) from November 2009 (pilot phase January 2009 to August 2011) to September 2014, when recruitment was suspended following concerns raised by the Data and Safety Monitoring Committee. The mean age of participants was 37 years (range 16–78 years). In total, 15% of TH patients and 18% of patients who received standard care alone were randomised within 12 hours of injury.

The adjusted common odds ratio (OR) for the primary statistical analysis of the GOSE score was 1.53 [95% confidence interval (CI) 1.02 to 2.30]. When the GOSE score was dichotomised, the adjusted common OR was 1.81 (95% CI 1.12 to 2.92). Both ORs were in favour of standard care alone.

Conclusion

In patients with ICP of > 20 mmHg after TBI, titrated hypothermia to reduce ICP led to worse functional outcomes. Future work should study targeted temperature management of < 38 °C and > 36 °C after acute brain injury.

Knowledge landscape after the Eurotherm3235 Trial

We searched RCTs to update the evidence base on the use of TH when administered to adult patients in intensive care following TBI. The main outcomes of interest were mortality, poor (unfavourable) outcomes and new pneumonia.

Secondary aims were (1) comparison of control groups; (2) early (< 24 hours from injury) compared with late (> 24 hours from injury) TH; (3) the effect of duration of follow-up on mortality outcomes; and (4) whether or not the date of publication had any effect on the outcomes of TH trials.

Search methods for identification of trials

Searches were not restricted by date or publication status. Foreign articles published in English were included. The following databases were searched from 1 January 2011 to 31 March 2016: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, PubMed and EMBASE. The dates were chosen to be complementary to, and have an overlap of 12 months with, the previous systematic review conducted by one of the co-authors; this was to capture any trials that were in the process of publication.

Other sources

Reference lists of all included trials and relevant review articles were hand-searched by the authors. When appropriate, authors were contacted directly for further information.

Methodological criteria for selection of randomised controlled trials

The inclusion criteria were that trials must (1) be RCTs, (2) investigate adult moderate (i.e. a GCS score of 9–12) or severe (i.e. a GCS score of ≤ 8) TBI and (3) investigate TBI that was sustained following an acute, closed head injury. The use of TH was the intervention of interest. RCTs that did not have two treatment arms with TH compared with a control group were excluded. For the purpose of this review, TH was defined as any intervention with the intention of reducing core body temperature to below the physiological norm (36 °C). The method of temperature reduction was noted during data extraction. Patient outcomes at follow-up were assessed using mortality and poor outcome data. There was a particular emphasis on outcomes recorded on a scale, for example, the GOS, Ranchos Los Amigos Scale or an equivalent scale. Poor outcome reporting includes mortality figures, as per the usual reporting methodology.

Results

The searches identified 21 trials, including data for two new trials. One trial included in the 2014 review has now been published with additional data. These trials enrolled 2299 patients. Only one trial did not include mortality data.

Mortality was reported in 20 studies. When the results of these 20 RCTs were statistically aggregated, there was a significant reduction in mortality in the TH group [risk ratio (RR) 0.84, 95% CI 0.74 to 0.96; $p = 0.01$].

Twenty-one trials reported on poor outcome involving 2286 patients. There were significantly more poor outcomes in the control group than in the TH group (RR 0.81, 95% CI 0.75 to 0.87; $p < 0.00001$). Analysis of the two studies deemed to be at low risk of bias showed that poor outcomes were more likely in the TH group (RR 1.16, 95% CI 1.02 to 1.32; $p = 0.03$). Conversely, analysis of the 19 studies with a high risk of bias combined showed significantly more poor outcomes in the control group than in the TH group (RR 0.70, 95% CI 0.64 to 0.77; $p < 0.00001$).

A subanalysis on mortality specifically assessed the methodology used for temperature management in the control groups. There was no significant difference in mortality between the TH group and the control group with controlled normothermia (RR 0.89, 95% CI 0.74 to 1.08; $p = 0.25$). However, there was significantly greater mortality in the no temperature control group than in the TH group (RR 0.81, 95% CI 0.68 to 0.97; $p = 0.02$).

The studies were analysed separately depending on whether they ensured that their control group was maintained at < 38 °C or included 38 °C within the 'normothermia' control range. Those studies that stated that they used controlled normothermia without specifying the temperature range were placed in the latter group. Studies that controlled temperature to < 38 °C showed no significant difference in mortality outcomes between the control group and the TH group (RR 1.01, 95% CI 0.82 to 1.32; $p = 0.73$). In contrast, in those studies that included 38 °C within the normothermia range, mortality was significantly higher in the control group (RR 0.61, 95% CI 0.44 to 0.87; $p = 0.005$).

Discussion

When the temperature of the control group was controlled (controlled normothermia) and fever was avoided, TH was no longer beneficial.

Conclusion

Overall, the results of this systematic review shed doubt on the outcome benefits of TH. Low-quality studies are more likely to show that TH improves mortality. In addition, this review highlights the importance of temperature management in the control group of TH trials and, in particular, the avoidance of fever.

Trial registration

This trial is registered as ISRCTN34555414.

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