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Andrews PJ, Sinclair HL, Rodriguez A, Harris BA, Battison CG, Rhodes JK, *et al*. Hypothermia for intracranial hypertension after traumatic brain injury. N Engl J Med 2015; [Epub ahead of print].

Use of hypothermia in medical practice dates back to the ancient Greek physicians who used it in patients of haemorrhage and trauma. In current medical practice, therapeutic hypothermia is largely used as a neuroprotectant in patients of out-of-hospital cardiac arrest and neonatal hypoxic-ischaemic encephalopathy. Its role in patients of traumatic brain injury (TBI) is conflicting. A meta-analysis in 2008 found a trend towards better outcome with hypothermia in TBI, if cooling was maintained for more than 48 h.[1] Eurotherm3235 (The European Study of Therapeutic Hypothermia [32–35°C] for intracranial pressure [ICP] reduction after TBI) was designed keeping in mind the lessons learnt from the past and to overcome the fallacies of previous trials.

It was a multicenter, randomised controlled trial that tested titrated therapeutic hypothermia to standard management to control raised ICP on patient outcome. The treatment options for raised ICP were stratified into three stages. Stage 1 interventions included mechanical ventilation, head elevation, analgesia ± muscle paralysis and intravenous fluids with/without inotropes to maintain a mean arterial pressure of ≥80 mmHg. It also permitted ventriculostomy with or without cerebrospinal fluid drainage/surgical removal of space-occupying lesions. Stage 2 treatment options included hyper-osmolar therapy and inotropes to maintain a cerebral perfusion pressure (CPP) ≥60 mmHg ± therapeutic hypothermia. Use of barbiturates was not allowed at this stage. Patients not responding to Stage 2 methods were treated with Stage 3 interventions including barbiturate therapy and decompressive craniectomy. All patients admitted to Intensive Care Unit (ICU) after TBI with ICP monitoring in place were screened. Two thousand four hundred and ninety eight patients from 55 centres in 18 countries were assessed for eligibility for inclusion in the trial, of which 387 patients from 47 centres were randomised. The trial included adult patients with primary closed TBI with an abnormal computed tomography scan of brain and an ICP >20 mmHg for ≥5 min resistant to Stage 1 therapy. The core temperature ≥36°C at the time of randomisation. Enrolment of patients was initially allowed for upto 72 h after injury but was increased to 10 days after injury, after the pilot phase, to include those with evolving brain swelling. An upper age limit of 65 years was also removed after the pilot phase to include older patients. Patients already receiving therapeutic hypothermia or barbiturate infusion, those unlikely to survive for next 24 h, temperature ≤34°C at hospital admission and pregnant were excluded. Patients randomised to control group received standard care whereas those randomised to study group received therapeutic hypothermia in addition to standard Stage 2 treatment to control raised ICP. Induction of hypothermia was done with 20–30 ml/kg of refrigerated 0.9% saline given over 20–30 min and maintained with the cooling technique available at the centre. Hypothermia was continued for a minimum of 48 h or as long as required to maintain ICP <20 mmHg. Guideline was provided for detection and treatment of shivering. Rewarming at a rate of 0.25°C/h was considered after a minimum period of 48 h if ICP was <20 mmHg, or if Stage 3 therapy was required. Outcome assessment was done using the Extended Glasgow Outcome Scale at 6 months. Other variables studied were 6 months mortality rate, ICP control, incidence of pneumonia and other serious adverse events (bleeding, cardiovascular instability, thermal burns, CPP <50 mmHg), length of ICU and hospital stay, modified Oxford Handicap Scale at 1 month, discharge or death and economics. The trial initially aimed to enrol a total of 1800 patients which was reduced to 600 patients after the pilot phase, but, recruitment had to be stopped in October 2014 for safety concerns. The study found that Stage 3 interventions were required in 54% and 44% patients in control and study group, respectively. Stage 2 treatment failure was seen less frequently in hypothermia group. Barbiturate infusion was used more frequently in the control group but not in patients who underwent decompressive craniectomy. A worse outcome was observed in the study group at 6 months (adjusted common odds ratio 1.53, $P = 0.04$). A favourable outcome occurred in 25.7% and 36.5% patients in hypothermia and control group, respectively ($P = 0.03$). Serious adverse events occurred more often in hypothermia group (33 events vs. 10 events). There was no significant difference based on the time from injury to initiation of hypothermia (<12 h vs. ≥12 h). The authors concluded that in patients of TBI with intracranial hypertension, use of therapeutic hypothermia along with standard care did not result in improved outcome than with standard

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care alone though there is a risk of bias since the trial was stopped early due to safety concerns.

Although therapeutic hypothermia has been studied in TBI earlier, none of the trials so far have been able to establish its neuroprotective role with certainty. Its ability to reduce ICP is known but improvement in patient outcome has not been established so far. A Cochrane meta-analysis (2009) of 23 trials concluded that there is no evidence that hypothermia is beneficial in TBI. It reduced unfavourable outcomes in low-quality trials only.[2] A more recent systematic review by Crossley *et al*., suggested that therapeutic hypothermia may be beneficial in TBI, but again, the majority of trials included were of low quality.[3] In a recent trial by Maekawa *et al*. compared prolonged mild therapeutic hypothermia (32–34°C) for ≥ 72 h and slower rewarming (<1°C/day) with fever control (35.5–37°C). They found no significant difference in the likelihood of poor neurological outcome between the two groups.[4] With conflicting evidence still continuing, the debate about the effectiveness of therapeutic hypothermia in TBI is likely to continue. The choice of this treatment modality in TBI largely remains individual and dependent on familiarity with cooling techniques, local expertise and protocols.

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Hypothermia for traumatic brain injury (TBI) has been tried in both adult and paediatric patients with equivocal results. Paediatric trials are relatively fewer in number and have not shown any consistent results and improved outcome.

TBI being a heterogenous condition is probably the reason behind the variable results with therapeutic hypothermia. Adelson *et al*. in 2005 concluded that moderate hypothermia (32–33°C) after severe TBI up to 24 h after is likely a safe therapeutic intervention.[1] Whereas, the cool kids trial by the same authors, a Phase 3 trial published in 2013, which enrolled patients within 6 h of injury to compare hypothermia (32–33°C for 48–72 h) followed by rewarming at 0.5–1.0°C every 12–24 h with normothermia (36.5–37.5°C) was terminated early for futility and found no difference in mortality or poor outcome between the two groups.[2]

This Phase 2 trial by Beca *et al*. included 8 Paediatric Intensive Care Units (PICUs) in Australia and New Zealand and 1 in Canada with an objective of performing a pilot study to assess the feasibility of conducting a Phase 3 trial of therapeutic hypothermia in children with severe TBI. The authors hypothesised that early and prolonged therapeutic hypothermia, with rate of rewarming guided by intracranial pressure (ICP) and cerebral perfusion pressure (CPP), will improve outcome. Patients were enroled from November 2006 to May 2010 with a 2–6 months period of suspension in between (due to Hutchison *et al*., showing that hypothermia therapy initiated within 8 h of injury and continued for 24 h did not improve neurological outcome and may increase mortality),[3] but, was later continued. Inclusion criteria were children 1–15 years of age with a Glasgow Coma Scale (GCS) <9 on mechanical ventilation and an abnormal computed tomography (CT) scan of brain. Children were excluded if they were not randomised within 6 h of injury, penetrating brain injury, fixed dilated pupils with GCS = 3, cervical spinal cord injury, more than mild developmental disability, an acute extradural haematoma evacuated, post-traumatic clinical seizure with a normal CT scan, refractory shock or nonaccidental injury. A total of 764 children were screened, 92 (12%) were eligible and 55 (7.2%) were randomised out of which 50 were managed as per protocol. A standard algorithm for treatment of intracranial hypertension in a tiered manner was used. Goals were an ICP of <20 mmHg and a CPP of >40–50 mmHg in <2 years age, >50 mmHg in <11 years of age and >60 mmHg in >10 years of age. Strict normothermia (36–37°C) was maintained in the control group for 72 h whereas in the study group, therapeutic hypothermia (32–33°C) was maintained for 72 h. Oesophageal temperature was monitored and servo controlled cooling blankets were used to control temperature. The study group patients were rewarmed at a rate of no more than 0.5°C/3 h, but, guided primarily by ICP and CPP. The primary endpoints studied were paediatric cerebral performance category at 12 months, eligibility and recruitment rates, protocol violations and major adverse events. Secondary outcomes were ICP and CPP during first 5 days and treatment required, duration of mechanical ventilation, PICU and hospital length of stay and adverse events (infections, bleeding, pancreatitis, acute respiratory distress syndrome,