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,

arrhythmias). Children in the hypothermia group took 0.9 h longer to reach the study site ($P = 0.02$). The median time to randomisation was approximately 5 h. In hypothermia group, the median time from injury to target temperature was 9.3 h and from randomisation to target temperature was 4.6 h. There was no difference in primary outcome at 12 months with 3 patients (12%) in normothermia group and 4 patients (17%) in hypothermia group having bad outcome ($P = 0.70$). During the cooling phase, a drop in heart rate of 23.4 bpm ($P < 0.001$) and a fall in ICP of 1.8 mmHg ($P = 0.02$) was noted. Hypothermia was maintained for a median of 93.5 h. No significant difference in mean arterial pressure (MAP) or CPP during cooling and in MAP, ICP or CPP during rewarming was observed. Hypotension occurred in 17% children in hypothermia group ($P = 0.05$), but, there was no difference in episodes of intracranial hypertension or low CPP. No difference in use of adjuvant therapies or any other secondary endpoint was seen between the two groups. The authors suggest that with a randomisation rate of 7.2% and an overall bad outcome rate of 14%, it may not be feasible to conduct a conventional large randomised controlled trial and that alternative trial types may be required.

A meta-analysis in 2013 by Ma *et al*. concluded that hypothermia may increase the risk of mortality and arrhythmias in paediatric TBI patients.[4] Similarly, another meta-analysis by Zhang *et al*. in 2015 found that therapeutic hypothermia in children with TBI may increase mortality and risk of arrhythmias and there is no evidence of an improvement in prognosis with its use.[5]

With lack of adequate evidence to support the use of therapeutic hypothermia as therapy in both adult and paediatric TBI patients, the current Brain Trauma Foundation (BTF) guidelines have a level III recommendation for use of hypothermia in TBI patients. A greater decrease in mortality is observed when target temperatures are maintained for more than 48 h in severe TBI. In paediatric patients, the BTF makes level II recommendation that moderate hypothermia (32–33°C) beginning within 8 h of injury for up to 48 h duration should be considered to reduce ICP and rewarming at a rate of >0.5°C/h should be avoided.

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Conflicts of interest

There are no conflicts of interest.

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