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# Hypothermia in neurocritical care patients other than cardiac arrest

Hypothermia (HT) is a cornerstone of neuroprotective strategies and has been used in critical care for acutely brain injured adult patients for many years. This review aims to discuss the clinical evidence supporting the use of HT in neurocritical care patients beyond care after cardiac arrest (CA), such as traumatic brain injury (TBI), acute ischaemic stroke (AIS), non-traumatic intracerebral haemorrhage (ICH) and subarachnoid haemorrhage (SAH). Despite promising results in small clinical trials and laboratory studies, HT did not improve outcome in large multicentre trials. Similarly, the use of HT as a specific intervention to treat secondary brain damage failed to improve outcome in humans. Despite these negative results, targeted temperature management (TTM) remains a crucial intervention in neurocritical care as part of the emerging principle of individualised medicine. Based on the pathophysiology of harmful effects associated with fever, the concept of normothermia has been implemented in most neurointensive care units to prevent periods of fever. In the following we will review the current status of HT as well as ongoing clinical trials of TTM (see summary in Table) and provide some thoughts for designing future studies.

From a conceptual point of view, mild HT (32–34°C) can be used as prophylactic intervention early after acute brain injury (ABI) or as a symptom-based treatment for e.g. refractory intracranial hypertension, brain oedema, vasospasm after SAH and other complications. If HT is used as specific therapy it is important to first prove that the resolution of such complications is in fact associated with improved functional outcomes before an intervention like HT with potential detrimental side effects is implemented. Though experimental data suggest a significant neuroprotective effect for TTM, large multicentre clinical trials investigating HT in ABI failed to demonstrate an unambiguous clinical benefit.

## Hypothermia as early prophylactic neuroprotective treatment

### *Traumatic brain injury*

TBI is a dynamic disease with distinct pathophysiologic mechanisms depending on the injury type, injury severity and the time elapsed since the initial trauma (Maas et al. 2017). Secondary injury mechanisms including excitotoxicity, neuro-inflammation, ionic fluctuations, necrosis and apoptotic cell death have been well characterised in preclinical studies. Most of these factors are sensitive to temperature changes and may be aggravated by intracranial or extracranial insults. HT has been used in the treatment of TBI for many years and can effectively ameliorate secondary injury. Despite promising results from experimental studies and small clinical trials (Polderman 2008), large multicentre trials failed to translate the putative benefits of HT into improved outcome in TBI patients (Clifton et al. 2001; 2011; Maekawa et al. 2015). A trend towards improved functional recovery was seen in TBI patients who were hypothermic on admission, suggesting that ultra-early initiation of HT may be important (Clifton et al. 2001). In the National Acute Brain Injury study: Hypothermia II (NABISH II) trial mean time to 35°C was reached after 2.6h and time to 33° was 4.4h (Clifton et al. 2011). However, enrolment was stopped for futility when interim analyses found no difference in mortality or neurological outcomes. Post-hoc analysis suggested a benefit for severe TBI patients with focal lesions undergoing haematoma removal, pointing to the pathophysiologic concept of reperfusion injury that may be ameliorated by HT (Clifton et al. 2012). The Hypothermia for Patients requiring Evacuation of Subdural Hematoma (HOPES) trial is currently investigating this hypothesis in TBI patients requiring emergent craniotomy (**clinicaltrials.gov/ct2/show/NCT02064959**). Based on the concept of ongoing secondary injury beyond 48h after severe TBI, long-term HT (4-6 d) was associated with significantly higher rate of favourable outcomes at 6 months when compared to short-term HT (1-3 d) in a single-centre trial including 215 severe TBI patients with cerebral contusion and intracranial hypertension (Jiang et al. 2006). Extended cooling over 5 days is currently explored in the Long-term Mild Hypothermia for Severe Traumatic Brain Injury (LTH-I) trial (**clinicaltrials.gov/ct2/show/NCT01886222; Lei et al. 2015**). In addition, the POLAR-RCT (Prophylactic

**Table.** Characteristics of selected ongoing clinical TTM trials in patients with acute brain injury (clinicaltrials.gov)

| | |
|---|---|
| **To Study the Effect of Early Cooling in Acute Subdural Hematoma Patients (HOPES) clinicaltrials.gov/ct2/show/NCT02064959** | |
| Status | Recruiting |
| Inclusion criteria | Non-penetrating traumatic brain injury |
| | Glasgow Coma Scale (GCS) motor score ≤5 (not following commands) |
| | Estimated or known age 22-65 years |
| | Acute subdural haematoma requiring emergent craniotomy within 6 hours of initial injury |
| | Estimated time of injury to time to reach temp. of 35°C<6 hrs |
| Study arms | Hypothermia (33°C) |
| | Standard care - normothermia (37°C) |
| Primary outcome | Glasgow Outcome Scale-Extended (GOSE) at 6 months |
| **Randomized Controlled Trial of Long-term Mild Hypothermia for Severe Traumatic Brain Injury (LTH-I) clinicaltrials.gov/ct2/show/record/NCT01886222** | |
| Status | Recruiting |
| Inclusion criteria | Age 18 - 65 years within 6 hours post injury |
| | Closed head injury |
| | GCS score 4 to 8 after resuscitation |
| | The intracranial pressure is more than 25 mmHg |
| | Cerebral contusion on computed tomographic scan |
| Study arms | Long-term mild hypothermia (34-35°C for 5 days) |
| | Normothermia (36-37°C) |
| Primary outcome | Glasgow Outcome Scale (GOS) at 6 months |
| **The Prophylactic Hypothermia Trial to Lessen Traumatic Brain Injury (POLAR-RCT) clinicaltrials.gov/ct2/show/NCT00987688** | |
| Status | Recruiting |
| Inclusion criteria | Blunt trauma with clinical diagnosis of severe TBI and GCS <9 |
| | Estimated age ≥ 18 and < 60 years of age |
| | The patient is intubated or intubation is imminent |
| Study arms | Early and sustained hypothermia (3°3C for 72 hours) |
| | Normothermia (37°C ± 0.5°C) |
| Primary outcome | Favourable neurological outcomes 6 months (GOSE 5 to 8) |
| **Safety and Feasibility Study of Targeted Temperature Management After ICH (TTM-ICH) clinicaltrials.gov/ct2/show/NCT01607151** | |
| Status | Unknown |
| Inclusion criteria | Spontaneous supratentorial ICH documented by CT scan within 18 hours after the onset of symptoms |
| | Admission to the Neuro-ICU |
| | Baseline haematoma >15cc with or without IVH |
| | Need for mechanical ventilation |
| Study arms | Hypothermia for 72h (32-34°C) |
| | Normothermia for 72h (36-37°C) |
| Primary outcome | Severe adverse events at 90 days |
| **Impact of Fever Prevention in Brain Injured Patients (INTREPID) clinicaltrials.gov/ct2/show/NCT02996266** | |
| Status | Recruiting |
| Inclusion criteria | Admitted with a primary neurological diagnosis of ischaemic stroke, intracerebral haemorrhage, or subarachnoid haemorrhage |
| | Prior to onset of acute symptoms, was considered functionally independent (mRS 0-2) |
| | Meets disease-specific criteria |
| Study arms | Prophylactic normothermia |
| | Standard care |
| Primary outcome | Fever Burden [Time Frame: Up to 14 days] |

Hypothermia Trial to Lessen Traumatic Brain Injury) trial aims to investigate the effect of early (prehospital) and sustained (72 h) mild HT on 6 months neurological outcomes in severe TBI patients, and titrates rewarming speed to intracranial pressure (ICP) and mean arterial pressure (MAP) (clinicaltrials.gov/ct2/show/NCT00987688); (Nichol et al. 2015). Current Brain Trauma Foundation guidelines recommend against the use of early (within 2.5h), short-term (48h post-injury) prophylactic hypothermia in severe TBI patients with diffuse injury (Level IIB; braintrauma.org). Despite a large number of studies, there remains no high-quality evidence that prophylactic hypothermia is beneficial in the treatment of patients with severe TBI (Lewis et al. 2017).

### *Acute ischaemic stroke*

In AIS mild HT is not effective to salvage neural tissue that has progressed irreversibly to infarction. HT can be directed at minimising the extent of secondary injury in the acute or subacute period of AIS. Based on animal data HT has a huge potential as a neuroprotective strategy when used early (within 2-3h), and mitigates ischaemic and reperfusion damage even when initiated up to 6 hours after ictus. However, clinical studies are limited by low patient numbers, slow recruitment, methodological issues and the occurrence of complications such as pneumonia and shivering, especially during HT in awake patients. So far, unequivocal efficacy of HT (33–35°C) has not yet been shown in AIS patients (Lyden et al. 2016; Piironen et al. 2014; De Georgia et al. 2004; Hemmen et al. 2010; Ovesen et al. 2013; Bi et al. 2011; Els et al. 2006), and the use outside clinical studies can currently not be recommended (Jauch et al. 2013; Ntaios et al. 2015).

The Cooling Plus Best Medical Treatment Versus Best Medical Treatment Alone for Acute Ischaemic Stroke (EuroHYP-1) trial explores the value of HT (34–35°C for 24h) within 150 minutes after start of alteplase administration and within 6 hours after stroke onset (van der Worp et al. 2014). The primary outcome is the degree of disability at 3 months measured by ordinal regression analysis of the modified Rankin Scale. This trial aims to recruit 800 patients and has recently reported safety based on preliminary analysis of 62 patients.

***Intracerebral haemorrhage***

Despite evidence from animal studies that HT attenuates perihaematoma oedema, inflammation and thrombin-induced injury and preserves blood-brain barrier integrity in ICH, we lack human data demonstrating improved neurologic outcome secondary to these beneficial effects of HT (Fischer et al. 2017). Two observational studies showed that mild prolonged HT (35°C over 8–10 d) had a favourable impact on perihaematomal oedema and ICP. However, no benefit for neurologic outcome was observed (Kollmar et al. 2010; Staykov et al. 2013). Although slow recruiting, the CINCH trial investigates HT at 35°C for 8 days in patients with primary ICH and large haematoma volume (25–64 mL) (Kollmar et al. 2012). A phase II prospective trial investigating 72h of mild HT (32–34°C) compared to normothermia (36–37°C) aims to include 50 supratentorial ICH patients (volume >15 ml) (clinicaltrials.gov/ct2/show/NCT01607151). For now, prophylactic mild HT is considered investigational in ICH patients and should only be applied in clinical trials (Hemphill et al. 2015). There is a strong need for prospective randomised-controlled trials further investigating the effect of hypothermia on perihaematoma oedema progression and neurological outcome.

***Subarachnoid haemorrhage***

Hypothermia has been used already in the 1950s as a neuroprotective strategy during aneurysm surgery in SAH patients (Botterell et al. 1956). The IHAST trial investigated HT (33°C) compared to normothermia in 1001 good-grade SAH patients during aneurysm surgery and failed to demonstrate an outcome benefit (Todd et al. 2005). Based on the reported non-significant increase in recovery, a recent Cochrane review, summarising 3 studies with 1158 participants, argued that it remains possible that intraoperative HT may be beneficial in good-grade SAH patients (Li et al. 2016). No conclusions can be drawn for poor-grade SAH patients.

Prophylactic HT was mostly tested in poor-grade SAH patients in single-centre studies underpowered to detect a difference in functional outcome (Choi et al. 2017; Gasser et al. 2003; Seule et al. 2009). An observational matched controlled study including 36 poor-grade SAH patients investigated early (<48h after ictus), mild (35°C), and prolonged (7±1 days) HT, and found a decreased rate of macro-vascular vasospasm and delayed cerebral ischaemia (DCI) (Kuramatsu et al. 2015). In a recent systematic review and meta-analysis including 9 studies the authors found a significant reduction in DCI favouring HT without an overall effect on mortality and morbidity (Yao et al. 2018). Further trials powered to detect differences in clinical outcomes are needed to investigate the potential role of HT after SAH in greater detail.

## Hypothermia as symptom-based intervention (to treat raised ICP)

HT was beneficial in controlling raised ICP and improving outcome in single-centre studies; however, large multicentre trials including the recently published Eurotherm3235 trial failed to confirm these findings for a heterogeneous TBI patient population (Andrews et al. 2015). This trial examined the effect of moderate HT (32–35°C) on ICP and neurological outcome and found that titrated HT successfully reduced ICP but did not improve functional outcome at 6 months. Interestingly, there were fewer occurrences of failure of stage 2 interventions to control ICP in the HT group, and stage 3 interventions (i.e. barbiturate coma but not decompressive craniectomy) were more often used in the control group. These data support the effectiveness of HT in reducing raised ICP. The recently published French guidelines recommend considering TTM at 34–35°C to lower ICP in TBI patients with refractory intracranial hypertension (Grade 2+) (Cariou et al. 2017). Based on expert consensus, TTM at 35-37°C may also be considered in patients with ICH and SAH to lower ICP (Cariou et al. 2017).

***Adverse effects associated with hypothermia***

Moderate HT is a reasonably well tolerated intervention when patients are meticulously managed in an intensive care environment by experienced clinicians. Vigilant monitoring for laboratory abnormalities, cardiac monitoring and standard critical care guidelines for monitoring of infections are recommended (Madden et al. 2017). Shivering is a physiologic thermoregulatory response and is related to increased metabolism, oxygen consumption, and increased energy expenditure, which could nullify the neuroprotective benefits of TTM. Therefore routine assessment (Badjatia et al. 2008) and aggressive treatment is recommended (Choi et al. 2011; Madden et al. 2017). Another important issue in the use of therapeutic HT is the rewarming phase. It has been shown that rapid rewarming is associated with worse outcome and rebound ICP increase (Schwab et al. 2001; Jiang et al. 2006). In order to avoid this detrimental complication patients with ABI should be rewarmed to normothermia as slowly as indicated on a case-to-case basis (Polderman and Andrews 2011).

## Normothermia

Acutely brain-injured patients commonly demonstrate periods of fever during the first few days after admission. Post-injury fever is associated with longer ICU stays and worse outcomes through aggravation of secondary brain injury mechanisms including excitotoxicity, increased oxygen consumption, pro-inflammatory response and increased vascular permeability leading to oedema formation with elevated ICP, increased ischaemic injury and cerebral vasospasm (Kilpatrick et al. 2000). Badjatia et al. reported a reduction in poor neurologic 12 months outcome after SAH in a case control study comparing aggressive temperature control to normothermia and conventional management of fever (Badjatia et al. 2010). Post-hoc analysis of the Japanese Brain Hypothermia (B-HYPO) study suggested a survival benefit of fever control in severe but not critical trauma patients pointing to the concept of normothermia, i.e. avoiding fever in TBI patients (Hifumi et al. 2016). Prophylactic interventions targeting normothermia have been shown to decrease the fever burden, and have been proven safe in haemorrhagic and ischaemic stroke patients (Broessner et al. 2009), and are currently under investigation in a prospective trial targeting 1176 patients (INTREPID trial, clinicaltrials.gov/ct2/show/NCT02996266). The goal of normothermia, avoiding fever, and aggressively treating fever has been suggested based on a systematic review in TBI patients and is recommended by a French expert panel reviewing the evidence for TTM in neurocritical care patients using the GRADE method (Madden and DeVon 2015; Cariou et al. 2017). TTM is therefore

implemented in most neuro-intensive care units including AIS and TBI to prevent periods of fever (Rincon et al. 2014).

## Summary and future perspective

The failure to translate the beneficial effect of HT observed in experimental studies to patients with ABI may reflect a limited knowledge of the multiple pathophysiologic mechanisms of secondary injury in the diverse brain pathologies. In this respect, multimodal neuromonitoring, although still mostly invasive, may help to provide insight into the pathophysiologic consequences of these conditions (Schiefecker et al. 2015). For example, increased brain temperature has recently been associated with cortical spreading depolarisations (CSD) in patients with TBI and spontaneous ICH (Schiefecker et al. 2017; Hartings et al. 2009). This is of interest because it is well known that the occurrence of CSD is extremely energy demanding and contributes to cortical lesion development following ABI (Hartings et al. 2017). This is further corroborated by the observation that clustered CSD were associated with metabolic distress and oedema development in patients with large ICH (Helbok et al. 2017). Considering the notable progress achieved by incorporating such a multimodal neuromonitoring system, this may open up the opportunity for providing individualised treatment and precision medicine in severely brain-injured patients in the future.

## Conclusion

Based on the current evidence the use of prophylactic HT is not recommended in ABI patients (not considering patients with cardiac arrest) and should only be applied in the setting of clinical trials. There is a role for HT as a symptom-based intervention to e.g. treat refractory intracranial hypertension. Further research is needed to characterise the magnitude and duration of temperature modulation after ABI required for improvement of neurologic outcome. Prevention of fever and aggressive fever treatment (i.e. concept of normothermia) is feasible and recommended by experts.

### *Conflict of interest*

Raimund Helbok received speaker 's honoraria of BARD Medical and ZOLL Medical and serves in the advisory board of the Intrepid trial (Bard Medical). Ronny Beer declares no conflict of interests. ■

### Abbreviations

ABI acute brain injury
AIS acute ischaemic stroke
CA cardiac arrest
CSD cortical spreading depolarisations
HT hypothermia
ICH intercerebral haemorrhage
IVH intraventricular haemorrhage
SAH subarachnoid haemorrhage
TBI traumatic brain injury
TTM targeted temperature management

## References

**For full references, please email editorial@icu-management.org or visit https://iii.hm/hwm**