



Hypothermia for the Management of Intracranial Hypertension in Severe Brain Trauma: The Paradigm is Broken?

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Worldwide, traumatic brain injury (TBI) comprises a combined incidence rate for all ages of approximately 350 per 100,000 person-years and is a leading cause of death and disability in trauma patients^{1,2}. The presentation of TBI varies from mild alterations of consciousness to a comatose state and death³. However, despite the existence of many classification systems, the simplest includes mild, moderate, and severe TBI, in which the nature of the injury and the impact on the patient's clinical condition is considered⁴. In the last decade, a clear trend has been demonstrated towards deterioration in patients with severe TBI, in which the whole brain is affected precisely because of the characteristics and degree of injury. This deterioration may be associated with a loss of autoregulation due to the lack of reactivity of cerebral vascular pressure, resulting in hyperemia, interstitial edema and subsequent intracranial hypertension (ICH)^{5,6}.

Normal intracranial pressure in adults is less than 15 mm Hg, values that remain above 20 mm Hg are considered pathological and are an indication for intensified treatment in patients with TBI⁷. It is important to consider that ICH can result from primary injury (hematoma expansion) or secondary damage (water accumulation, impaired autoregulation, ischemia, and contusion expansion). This is associated with high mortality rates, so multiple early, stepwise, and rescue management strategies have been proposed for its control, which is aimed at preventing secondary injury by avoiding hypotension, hypoxia and maintaining adequate cerebral perfusion pressure (CPP). Targeted treatment is essential and may include cerebrospinal fluid (CSF) drainage, use of hyperosmolar therapies, induction of hypothermia, hyperventilation, administration of barbiturates, or performance of decompressive surgery^{2,8}.

Therapeutic hypothermia (TH) is one of the few neuroprotectants that has moved from preclinical work to clinical use. For example, it was previously used to prevent brain damage during cardiac surgical procedures, but more recently it has also been used to improve both neurological and physical out-

comes after sudden cardiac arrest⁹). Based on rodent studies, it has been found that angiogenesis and neurogenesis are stimulated by brain cooling, significantly attenuating brain infarction induced especially in the context of TBI¹⁰). Likewise, multiple analyses have led to consider TH as an attractive treatment strategy for severe TBI as it confers several theoretical benefits, including the ability to reduce ICP and increase CPP¹¹). TH has been widely investigated as neuroprotection and treatment of ICH, however, in the setting of severe TBI it has had mixed results. Two large studies (POLAR and Eurotherm 3235) represent strong scientific evidence against its use^{12,13}). But should it be completely discarded? Temperature changes play a critical role in neuronal vulnerability after TBI, and relatively small reductions in temperature may be effective in controlling ICH. Early therapeutic hypothermia can reduce histopathological damage by attenuating the severity of diffuse axonal injury, decreasing brain metabolism and oxygen consumption, reducing edema, stabilizing the blood-brain barrier (BBB), and promoting the survival rate in the acute stage of TBI^{14,15}). In addition, it reduces susceptibility to post-traumatic seizures and decreases the inflammatory response to injury¹⁴). A meta-analysis reported that compared with adults who remained normothermic, those who underwent TH were associated with reduced mortality and improved neurological outcome¹⁶). However, since the central nervous system (CNS) is a complex circuit, the use of hypothermia as a management strategy may impact outcomes 6 months after the event. The Eurotherm3235 and POLAR studies have attempted to improve the available scientific evidence and constitute two major tools against the use of prophylactic and therapeutic hypothermia in patients with severe TBI, respectively (Table 1).

Eurotherm3235 evaluated the efficacy of TH plus standard care versus standard care alone and, during the first 4 days after randomization, the TH group significantly reduced elevated ICP levels, with less requirement for second or third level therapies. However, there was no significant difference in ICP in both groups on day 7 after randomization. Regarding the outcomes evaluated at 6 months, TH showed a lower percentage of favorable results and higher mortality¹²). There is currently controversy as to the period of hypothermia that should be used, and in this study, it may not have been long enough (> 48h) to show any benefit in improving the outcome of patients with severe TBI. A recent randomized multicenter trial using a longer period of hypothermia (up to 5 days) reported a higher percentage of favorable outcomes and a lower proportion of mortality at 6 months in the intervention group (TH) compared to the normothermia group¹⁷). Although these results were not statistically significant, not all patients in the hypothermia group were able to cool to the target temperature of 34-35°C. Higher quality studies with longer TH periods may rep-

Table 1. Main characteristics of the studies analyzed

Study	Eurotherm 3235 Andrews et al., 2015 ¹² (n=387)	The POLAR randomized clinical trial Cooper et al., 2018 ¹³ (n=511)
Countries involved	47 centers in 18 countries (United Kingdom, Belgium, Germany, Greece, Estonia, Hungary, India, Ireland, Italy, Portugal, Russia, Saudi Arabia, Spain, Netherlands, United Arab Emirates)	Five out-of-hospital or paramedic agencies and 14 emergency departments in 6 countries (Australia, New Zealand, France, Switzerland, Saudi Arabia, Qatar)
Selection period	November 2009-October 2014	December 2010-May 2018
Inclusion criteria	<ul style="list-style-type: none"> -Age > 18 years -Closed primary TBI -ICP > 20 mmHg for at least 5 min after stage I treatments, without an obvious reversible cause -TBI occurred no more than 10 days before -Availability of a cooling device or technique > 48 hours -Central temperature $\geq 36^\circ\text{C}$ (at the time of randomization) -Abnormal CT of the brain 	<ul style="list-style-type: none"> -Age ≥ 18 and <60 years -Blunt trauma with clinical diagnosis of severe TBI and GCS <9 -Actual or imminent endotracheal intubation

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Table 1. Continued

Study	Eurotherm 3235 Andrews et al., 2015 ¹² (n=387)	The POLAR randomized clinical trial Cooper et al., 2018 ¹³ (n=511)
Exclusion criteria	<ul style="list-style-type: none"> - Patient already receiving treatment with induced hypothermia - Administration of barbiturate infusion prior to randomization - Low probability of survival during the next 24 hours (e.g, bilateral fixed dilated pupils) - Temperature <34 °C at hospital admission - Pregnancy 	<p><i>Exclusion criteria in out-of-hospital setting</i></p> <ul style="list-style-type: none"> - Clinical diagnosis of drug or alcohol intoxication as the predominant cause of coma - Non-randomization within 3 hours after the estimated time of injury - Estimated transport time to the study hospital > 2.5 hours - Suitable for intubation without drugs - Systolic blood pressure <90 mm Hg - Heart rate > 120 bpm - Cardiac arrest - GCS score = 3 + non-reactive pupils - Penetrating neck/torso injury - Known or obvious pregnancy - Receiving hospital is not a study site - Evidence of anticoagulant therapy - Caregiver dependent due to a pre-existing neurological condition <p><i>Exclusion criteria in the emergency department</i></p> <ul style="list-style-type: none"> - Presence of previous criteria - Clinically significant bleeding likely to require intervention - Positive pregnancy test in urine or blood - In the opinion of the treating physician, "cooling" is not the best option
Randomization	Therapeutic hypothermia plus standard care vs. standard care	Early prophylactic hypothermia vs. normothermia
Hypothermia definition	32 to 35 °C	33 to 35 °C
Time (TBI - onset of hypothermia)	Up to 10 days after injury	Up to 3 hours after injury.
Duration of intervention	48 hours - until needed to control intracranial pressure	≥72 hours - maximum period of 7 days.
Reheating	If the intracranial pressure was less than 20 mm Hg, it was increased 0.25 °C / hour	If the intracranial pressure was less than 20 mm Hg, it was increased 0.25 °C / hour
Primary untie at 6 months	Hypothermia vs. control: Favorable results (GOS-E of 5 to 8) 25.7% vs. 36.5%	Hypothermia vs. control: Favorable results (GOS-E of 5 to 8) 48.8% vs. 49.1%
Secondary results	Hypothermia vs. control: Mortality at 6 months: 32.2% vs. 25.2%	Hypothermia vs. control: Mortality at 6 months: 21.1% vs. 18.4.5%

GCS: Glasgow come score, GOS-E: The glasgow outcome scale extended, TBI: Traumatic brain injury.

resent an important consideration for future evaluation, as some hypotheses suggest that cytotoxic edema and intracellular neurotoxicity cascades may be attenuated at the peak which is around day 5 in TBI patients^{11,17}.

Regarding the use of TH as a rescue strategy in severe and refractory ICH, it has been very little evaluated, however, some analyses by subgroups of patients with an initial ICP ≥ 30 mm Hg, found that long-term mild TH significantly increased the favorable outcome at 6 months without raising the incidence of severe complications such as pneumonia, hypokalemia, thrombocytopenia and arrhythmias¹⁷. Likewise, the rewarming time at Eurotherm ($0.25^{\circ}\text{C}/\text{hour}$), which is equivalent to 3°C in only 12 hours, could have influenced the results. One analysis found that slow rewarming at a rate of $< 1^{\circ}\text{C}/\text{day}$ with a rewarming time of ≥ 48 hours significantly improved neurological outcomes at 6 months after mild TH in patients with severe TBI and evacuated hematoma¹⁸. So a slower rewarming period than that used in Eurotherm would form a critical element when using TH in patients with TBI

On the other hand, the POLAR-RT study did not evaluate hypothermia as a therapeutic strategy for ICH, but rather as an early prophylactic utility for TBI. This study compared prophylactic hypothermia (PH) vs. normothermia and reported good ICP control during the first 4 days post-randomization, however, is found at 6 months a lower percentage of favorable outcomes and a higher proportion of mortality in the hypothermia group¹³. A recently published review that included the POLAR study in its meta-analysis¹⁹ represents valuable evidence. This analysis demonstrates the importance of specific cooling parameters such as cooling temperature, cooling duration, and rewarming rate, and considers that these were a major limitation of the POLAR study, as they were only achieved in less than half of the patients who received PH, achieving a moderate level of cooling¹⁹ (Table 2).

This review builds on a previous meta-analysis evaluating the effect of cooling parameters in TBI patients, which found that for trials that accurately reported the cooling protocol, there was a reduction in the odds ratio of death in the TH group compared to no

cooling, concluding that TH was beneficial only if the cooling index (COIN) was sufficiently high (longer cooling and at temperature $\leq 0.25^{\circ}\text{C}/\text{h}$)²⁰. Likewise, when data from the POLAR study were included in a new meta-analysis published recently, the results were similar to the previous study and indicated that the use of hypothermia significantly decreased mortality in severe TBI only in cases where COIN was high¹⁹. Thus, it is possible that the decrease in COIN masks some of the outcomes evaluated in the POLAR study (favorable PH and 6-month mortality outcomes).

Taking into account the effect of hypothermia in reducing brain metabolism, considering it in the management of ICH in patients with TBI could play an important role. A clinical trial evaluating patients with severe TBI found that inducing TH aimed at achieving a 50-60% reduction in cerebral metabolic rate significantly reduced patient mortality²¹. This was not considered in the Eurotherm and POLAR studies and could constitute the missing gap to evaluate the benefit of TH in patients with severe TBI and their 6-month outcomes

The Eurotherm 3225 and POLAR studies show that TH and PH control ICP, but without an impact on outcomes. This leads to the idea that TBI is a changing and very diverse entity, where ICP control is important but not sufficient to improve outcomes. It is still premature to abandon the use of TH and PH in patients with severe TBI as questions and controversies remain. An evaluation of methods to induce hypothermia, as well as of multiple combinations of treatments used in the management of ICH, is needed to determine possible synergistic effects with maximal benefits. Considering the available evidence, TH should not be considered a treatment in all patients with ICH, but in our opinion, it is a very good option in selected cases (ICH > 30 mm Hg) or as a rescue strategy. In addition, to have a wider field of application for its therapeutic and prophylactic use, there is a clear need for more studies that consider prolonged mild hypothermia (> 5 days), slow rewarming ($< 1^{\circ}\text{C}/\text{day}$) and adequate cooling rate (high) or establish situations that may influence mortality and medium-long term outcomes.

NOTES

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Table 2. Comparison between the Eurotherm 3235 and POLAR-RCT studies regarding the use of hypothermia in the management of intracranial hypertension in traumatic brain injury

Variables studied	Results
Cooling duration	72,2 hours
Body cooling temperature	33-35 °C
Overheating rate	$\leq 0,25^{\circ}\text{C}/\text{hour}$
No. of patients (%)	124 (48%)
COIN Subgroup	Moderate

COIN: Cooling index.

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