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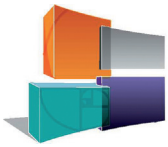

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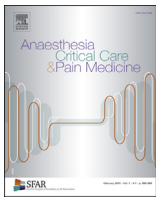

Editorial

Therapeutic hypothermia after traumatic brain injury: Wrong hypotheses may lead to specious interpretations

The POLAR study by Cooper et al adds to the growing evidence that early prophylactic hypothermia may not be useful for patients with severe traumatic brain injury (TBI) [1]. Three other high-grade randomised controlled trials showed that therapeutic hypothermia (TH) did not improve neurologic outcome after TBI (see Table 1) [1–4]. Instead of abandoning this procedure from this basis, we should acknowledge that:

- there was a confusion in the use of prophylactic versus therapeutic hypothermia in these studies since one trial used hypothermia to treat patients with high intracranial pressure [2];
- only a deep level of hypothermia (32–35 °C) was tested in the intervention group; and;
- there was no temperature correction for $PaCO_2$ measurements, where $PaCO_2$ is a major factor influencing brain perfusion.

In experimental models of TBI, TH was constantly found to have neuroprotective properties [5]. Meanwhile, TH failed to demonstrate beneficial effects on neurologic outcome in patients with TBI. The absence of benefits of profound TH uniformly applied in TBI patients does not question the use of targeted control of temperature. Deleterious effects of hyperthermia are documented including causing high intracranial pressure [6,7]. Each in-charge physician should be aware of techniques for the targeted control of temperature. Indeed, high brain temperature is common after TBI, independently of any infectious process. Patients with TBI were found to have one degree Celsius difference between central temperature and brain temperature. This difference may be explained by thermoregulation disturbance, by thalamic lesions and/or by the activation of post-traumatic biochemical pathways such as glycolysis.

The occurrence of hypothermia-related side effects may be related to the depth level and/or to the rate of cooling. Possible benefits of TH might have been balanced by deleterious side effects at 33 °C such as hypovolaemia [8], immunosuppression [9], or cardiac impairment [10]. No study has tested the impact of progressive cooling down to 35 °C, which may not induce these side effects.

The issue regarding masked hyperventilation and TH had never been addressed [11]. All of the clinical trials used the alpha-stat management, i.e. no correction of $PaCO_2$ for temperature. Accordingly, TH may be seen as a therapy for controlling intracranial pressure through masked hyperventilation and hypocapnia. This phenomenon is related to increased CO_2 solubility into the blood and the decrease of global metabolism by hypothermia. Such reduction in $PaCO_2$ can then induce ischemic lesions and worsen the neurologic outcome [12]. The use of a pH-stat management, i.e. corrected $PaCO_2$ for temperature, would be appropriate to rule out potential confounding factor such as hypocapnia and assess the real impact of TH on outcome.

Finally, prophylactic hypothermia should be abandoned after TBI since this strategy does not improve neurologic outcome while inducing deleterious systemic side effects. The failure of deep hypothermia does not mean that controlling temperature is not important after TBI. Fever is associated with elevated ICP and patients with TBI should be maintained between 36 and 37 °C with adequate cooling techniques. The use of moderate hypothermia

Table 1
Main randomised controlled trials investigating the effect of therapeutic hypothermia in adults after traumatic brain injury.

Study	Sample size (NT vs. TH)	Targeted temperature	Duration of TH	Speed of rewarming	Effect on ICP	Odds ratio for bad neurologic outcome at 6 months
Clifton et al, 2001	193 vs. 199	33°C	48h	0.5 °C/2H	Yes	OR = 1.0 (95% CI, 0.8–1.2)
Clifton et al, 2011	45 vs. 52	33°C	48h	0.5 °C/2H	Yes	OR = 1.08 (95% CI, 0.76–1.58)
Andrews et al, 2015	192 vs. 195	32-35°C	48h-Day 7	0.5 °C/2H	No	OR = 1.53 (95% CI 1.02–2.30)
Cooper et al, 2018	266 vs. 245	33°C-35°C	72h-Day 7	0.5 °C/2H	No	OR = 0.99 (95% CI, 0.82–1.19)

NT: normothermia; TH: therapeutic hypothermia; ICP: intracranial pressure; OR: odds ratio.

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(35 °C) to control ICP has not been studied yet and may warrant further investigation. Correction of PaCO2 according to temperature will have to be applied to correctly address this issue.

Disclosure of interest

The authors declare that they have no competing interest.

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