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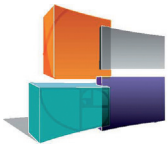

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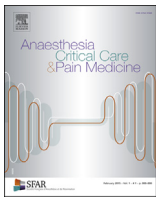

Editorial

Prophylactic hypothermia for traumatic brain injury patients: It is not cool to be cooled

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Traumatic Brain Injury (TBI) remains a major health and economic burden. Epidemiologic data predicted that the burden of TBI will out-pass many diseases as a major cause of death and disability within the coming years. Despite a tremendous effort made by the scientific and medical community mortality and disability caused by TBI remain important over the last decade [1]. Nearly one-fourth of severe traumatic brain injured patients will die during their hospital stay and less than a half of the survivors will have a favourable neurological outcome [2]. Improving survival and neurological recovery are therefore a medical and economic issue.

During the initial phase, the clinical state of the patient may worsen within hours after the initial insult. Indeed, if TBI induces direct lesions during the initial traumatism (so called primary lesions), secondary lesions will start appearing within minutes after the traumatism [3]. As primary lesions are irreversible, the goal of the medical team is to limit or avoid secondary insults [4]. These secondary insults are mainly caused by the decrease of blood flow in the brain tissue surrounding the initial lesion and by the activation of the inflammatory response [5,6]. Therefore, symptomatic treatment of hypotension and hypoxemia may decrease mortality and morbidity.

Therapeutic hypothermia has been suggested as an adjunct treatment to prevent neuronal death and to avoid secondary brain insult after traumatic brain injuries. Hypothermia decreases cerebral metabolic requirements and intracranial pressure, reduces blood–brain barrier permeability, excitotoxicity from glutamate release and inflammatory response [7]. Experimental studies have demonstrated a protective effect of therapeutic hypothermia during brain injury. Although, translation of these findings into clinical practice are yet to be demonstrated.

Only few high quality randomised controlled trial tested the hypothesis that early induction of mild therapeutic hypothermia [i.e.: Prophylactic hypothermia (PHT)] could improve patient outcome. The first study published by Marion et al. in 1997 in the New England Journal of Medicine showed, on a small sample of patients, that 24 hours of moderate PTH may have a protective effect [8]. These encouraging results weren't confirmed by Clifton and co-workers in 2001 [9]. The study randomised 396 patients in two groups, normothermia and PTH during 48 hours. This study did not demonstrate a protective effect of PHT and patient in the hypothermic group had a higher rate of complications. Clifton and co-workers repeated a similar study in 2011 but it had to be prematurely terminated for futility after randomizing 232 patients [10]. Even if it is difficult to draw conclusion from this study, its results didn't show a protective effect of PHT but reported a higher rate of complications in the hypothermic group. The criticism that could be addressed to these studies was that the duration of hypothermia was pre-determined and the rewarming wasn't guided by the patient's intracranial pressure.

A recent meta-analysis pooled 41 studies in adult patients representing 3109 patients [11]. This meta-analysis concluded that PHT had a protective effect for TBI patient with an improvement of survival and neurological outcome. The optimal duration of the HT seemed to be 72 hours. However most of the studies included in this meta-analysis were considered of poor methodological quality. Thus, the clinical data remained conflicting.

Therefore, a well-designed randomised clinical trial addressing the pitfall of the previous studies was still needed. The Prophylactic hypOthermia trial to Lessen trAumatic bRain injury (The POLAR study) is an international randomised trial designed to answer if early prophylactic hypothermia with the tolerance to rewarming monitored by the ICP may improve neurological outcome in sever TBI patients (GCS $<$ 8 and abnormalities on head CT scan) [12]. In this study patients were enrolled in the out of hospital setting or on arrival at the hospital and cooled to 33 °C as early as possible. Targeted temperature was planned to be achieved within the 6 hours after trauma and maintained at least for 72 hours. Intracranial pressure was monitored and assessed during rewarming. If ICP rose during rewarming the patient was cooled again to 33°c. Duration of hypothermia could last up to 7 days depending on the intracranial hypertension status of the patient.

511 TBI patients were enrolled in the study. The results of the trial showed that early hypothermia did not improve long-term functional outcomes and any of the secondary outcomes, including

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mortality at hospital discharge and at 6 months. Moreover, in the per-protocol and as-treated analyses, there was an increased risk of pneumonia among those who received hypothermia compared with patients who were not cooled. A major limitation could be addressed in the study: patients were enrolled in the study regardless the level of intracranial pressure, thus the targeted temperature wasn't reached in 27% of the patients in the intervention group and duration of hypothermia was less that 72 hours in 33% of the patients. Therefore, the results of the study have to be carefully analysed.

The POLAR study is the fourth well-randomised controlled trial testing the effect of mild prophylactic hypothermia in TBI. It is the largest trial on the subject to date. The results of the POLAR study are in line with the previous studies published and therefore it seems reasonable to conclude that early prophylactic mild hypothermia should not be performed in all TBI patients. On the other hand, the effect of therapeutic hypothermia to lower intracranial hypertension still needs more investigation in TBI patients with refractory intrcranial hypertension.

The Eurotherm 3235 [13] study published in 2015 investigated the effect of mild hypothermia in TBI patients with ICP above 20 mmHg despite initial optimal medical first line of treatment. This study was terminated prematurely because of concerns of a potential harm of hypothermia in the intervention group. This study is a step further in the evolution of TBI patients compared to POLAR as hypothermia aimed this time to lower ICP. Criticisms address to this study was that treatment differed between the two groups once patients randomised. If the Eurotherm 3235 brings new information on the indication of therapeutic hypothermia during TBI, the conclusion of the study needs to be cautiously taken in account.

Moderate hypothermia during treatment of TBI patient decreases ICP but yet failed to improve patient's outcome. The conflicting results between animal models and clinical data stress the fact that we need more data on the effect of hypothermia on human brain metabolism and blood flow in order to design an intervention that may benefit to the patient. Designing a clinical trial for TBI patients is very complex as the population is heterogeneous and and also because treatments are not standardised from one centre to another even though specialised neurointensive care centres follow international guidelines. We can also question if the target of the intervention in TBI clinical trials is relevant: aiming to decrease or normalise ICP may not be as relevant as we think. Aiming to ensure a normal cerebral blood flow or metabolism may be more accurate but increases the level of difficulty of bedside interpretation and clinical trial design.

From the most recent literature we can conclude that more studies are needed to investigate the effect of therapeutic hypothermia in TBI in order to define its indication. Nonetheless, in the light of the recent studies we can conclude that early prophylactic mild hypothermia shouldn't be considered as a first line treatment for TBI patients. Patients with refractory intracranial hypertension may be eligible to be treated by mild therapeutic hypothermia but more evidences are required to ensure the benefit and harmlessness of this intervention.

Disclosure of interest

Olivier Huet declares a conflict of interest with Edwards Life Sciences.
The other author declares that she has no competing interest.

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