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Therapeutic Hypothermia in Traumatic Brain Injury

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1. Introduction

Traumatic brain injury (TBI) is a major source of death and severe disability worldwide. In the USA alone, this type of injury causes 290,000 hospital admissions, 51,000 deaths, and 80,000 permanently disabled survivors [1,2]. Intracranial hypertension develops commonly in acute brain injury related to trauma [3,4]. Raised Intracranial pressure (ICP) is an important predictor of mortality in patients with severe TBI, and aggressive treatment of elevated ICP has been shown to reduce mortality and improve outcome [4-11]. Guidelines for the Management of Severe TBI, published in the Journal of Neurotrauma in 2007 [12] make a Level II recommendation that ICP should be monitored in all salvageable patients with a severe TBI (Glasgow Coma Scale [GCS] score of 3–8 after resuscitation) and an abnormal computed tomography (CT) scan. ICP monitoring is also recommended in patients with severe TBI and a normal CT scan if two or more of the following features are noted at admission: age over 40 years, unilateral or bilateral motor posturing, or systolic blood pressure < 90 mm Hg (Level III recommendation). Furthermore, ICP should be maintained less than 20 mmHg and cerebral perfusion pressure (CPP) between 50 and 70 mmHg (Level III).

As in ischemia–reperfusion injuries, the acute post-injury period in TBI is characterized by several pathophysiologic processes that start in the minutes to hours following injury and may last for hours to days. These result in further neuronal injury and are termed the secondary injury. Cellular mechanisms of secondary injury include all of the following: apoptosis, mitochondrial dysfunction, excitotoxicity, disruption in ATP metabolism, disruption in calcium homeostasis, increase in inflammatory mediators and cells, free radical formation, DNA damage, blood-brain barrier disruption, brain glucose utilization disruption, microcirculatory dysfunction and microvascular thrombosis [13-50]. All of these processes are temperature dependent; they are all aggravated by fever and inhibited by

hypothermia [13-50]. In addition, several studies have shown that development of fever following TBI is closely linked to intracranial hypertension and worsened outcome [51-53].

Clinical trials of hypothermia and temperature management for severe traumatic brain injury are divided into trials in which hypothermia is used to treat elevated intracranial pressure and those in which hypothermia is intended as a neuroprotectant, irrespective of intracranial pressure. In this article, we will review the current clinical evidence behind therapeutic hypothermia for the treatment of intracranial hypertension (ICH) in severe TBI patients, as well as therapeutic hypothermia as a neuroprotectant in severe TBI.

2. Methods

We queried the Medline database with the MeSH terms “Hypothermia, induced,” “Fever,” “Intracranial Hypertension”, and “Traumatic Brain Injury” from 1993 till 2011. We utilized both PubMed and OVID to maximize database penetration. We searched the Cochrane Database of Systematic Reviews. We also hand searched bibliographies of relevant citations and reviews. Inclusion criteria were double-blind, placebo-controlled, randomized controlled trials (RCTs), observational studies or meta-analyses of therapeutic hypothermia for TBI patients in which ICPs are monitored. We limited the search to human literature; We did not limit language, but we extracted studies that involved only adult subjects excluding studies on the pediatric population. Information extracted included number of patients, ICP, length of cooling, length of re-warming, outcome, complications, methods used to control ICP and the quality of each study. We reviewed the literature pertaining to pathophysiology of Traumatic Brain Injury. We also reviewed the literature pertaining to major published guidelines in this area.

3. Intracranial hypertension in TBI

In comatose TBI patients with an abnormal CT scan, the incidence of ICH was 53–63% [75]. Patients with a normal CT scan at admission, on the other hand, had a relatively low incidence of ICH (13%). However, within the normal CT group, if patients demonstrated at least two of three adverse features (age over 40 years, unilateral or bilateral motor posturing, or systolic BP < 90 mm Hg); their risk of ICH was similar to that of patients with abnormal CT scans [75]. ICP is a strong predictor of outcome from severe TBI [5,6, 9,76-78]. Because of this, ethically a randomized trial of ICP monitoring with and without treatment is unlikely to be carried out. Similarly, a trial for treating or not treating systemic hypotension is not likely. Both hypotension and raised ICP are the leading causes of death in severe TBI. Furthermore, several studies have shown that patients who do not have ICH or who respond to ICP-lowering therapies have a lower mortality than those whose ICH does not respond to therapy [4-11, 79-82]. As a result, Guidelines for the Management of Severe TBI recommend that treatment should be initiated with ICP thresholds above 20 mm Hg (level II) as well as target a cerebral perfusion pressure (CPP) within the range of 50-70 (level III) [12]. Prevention and/or treatment of ICH is commonly accomplished by employing a

Reference	No. of patients	Length of cooling	ICP(norm)	ICP(Hypo)	Length of rewarming	Outcome	Complications of hypothermia
Shiozaki et al, 1993	33	48 hrs	35.4	25 (p<0.01)	24 hrs	6 month survival(50 % vs 18 %, p<0.05) Death from uncontrolled ICH(31% vs 71 %, p<0.05)	No difference
Marion et al, 1993	40	24 hrs	ICP > 20 (25 %)	ICP > 20 (13 %) (p<0.001)	12 hrs	3 month good GOS (60 % vs 40 %, p < 0.24)	No difference
Marion et al, 1997	82	24 hrs	19.7	15.4 (p=0.01)	12 hrs	12 month good neurologic outcome (62 % vs 38 %, p=0.05)	Elevated PTT, decreased potassium
Jiang et al, 2000	87	3 - 14 days	29.6	18.9 (P < 0.01)	1°C/hr	1 yr good GOS (46.5 % vs 27.3 %, p < 0.05) 1 yr mortality (25.6 % vs 45.5 %, p < 0.05)	--
Clifton et al, 2001	392	47 hrs	ICP > 30 (59%)	ICP > 30 (41%) (p=0.02)	18 hrs (0.25°C/hr)	No difference	Hypotension, bradycardia
Polderman et al, 2001	41	n/a	36	15 (p < 0.01)	n/a	No difference	Hypomagnesemia, hypocalcemia, hypokalemia, hypophosphatemia
Polderman et al, 2002	136	4.8 days	37	< 20 (p < 0.01)	1°C/12hrs	6 m good GOS (15.7 % vs 9.7 %, p<0.02) Mortality (62 % vs 72 %, p<0.05)	arrhythmias
Gal et al, 2002	30	72 hrs	18	12 (p=0.0007)	passive	6 m good GOS (87% vs 47%)	---
Zhi et al, 2003	396	1-7 days (mean = 62 hrs)	26.9	14.8 (p<0.05)	16-20 hrs (1°C/4hrs)	6 m Good GOS(38.8% vs 19.7%, p<0.05) Mortality (25.7% vs 36.4%, p<0.05)	hypokalemia
Smrcka et al, 2005	72	72 hrs	Primary (18.9) Extracerebral (16.6)	Primary(10.8) (p < 0.0001) Extracerebral (13.2)(p =0.1)	passive	Primary(6 m GOS: p=0.44) Extracerebral (6 m GOS: 3 to 5 ,p= 0.0006) Total 6 m good GOS(85% vs 48.5%)	bradycardia
Qiu et al, 2005	86	3-5 days	24 hrs:32.6 48 hrs:34.8 72 hrs:31.8	27.3 (p <0.05) 29.4 (p <0.05) 26.4 (p <0.05)	Passive (up to 24 hrs)	2 yr good GOS (65% vs 37%, p<0.05) Mortality (25.6% vs 51.2%, p<0.05)	Pneumonia, thrombocytopenia
Jiang et al, 2006	215	2 days vs 5 days	28(2 day hypothermia)	18(5 day hypothermia)	1°C/hr	6 m good GOS(43.5% in 5 day group vs 29% in 2 day group, p < 0.05)	More rebound increase in ICP in 2 day group (p < 0.05) Pneumonia and arrhythmias (similar)
Qiu et al, 2007	80	4 days	24 hrs:25.8 48 hrs:25.9 72 hrs:24.6	23.5 (p=0.00) 24.6 (p=0.00) 22.5(p=0.003)	Passive(10- 24 hrs)	1 yr good neurologic outcome GOS (70% vs 47.5%, p=0.041)	Pneumonia, thrombocytopenia

GOS = Glasgow Outcome Score

Table 1. Effects of Hypothermia on intracranial pressure and outcome in patients with severe Traumatic Brain Injury: Randomized Controlled Trials

progression of therapeutic approaches that are efficacious in controlling ICP and uniformly believed to be easily applied with minimal or rare negative side effects. These measures include elevation of the head of the bed, avoiding hypotension, hypoxia, and hypercapnea or prolonged hypocapnea, intravenous sedation and analgesia, episodic administration of hyperosmolar agents (mannitol, hypertonic saline), and CSF drainage [12]. Reviewing the evidence behind all these aforementioned therapies is beyond the scope of this review, but the evidence of efficacy for all of these treatments is variable at best. They are recommended not so much because there is clear-cut proof of morbidity or mortality benefit but because they are deemed treatments without significant downside.

4. Therapeutic hypothermia for ICP control

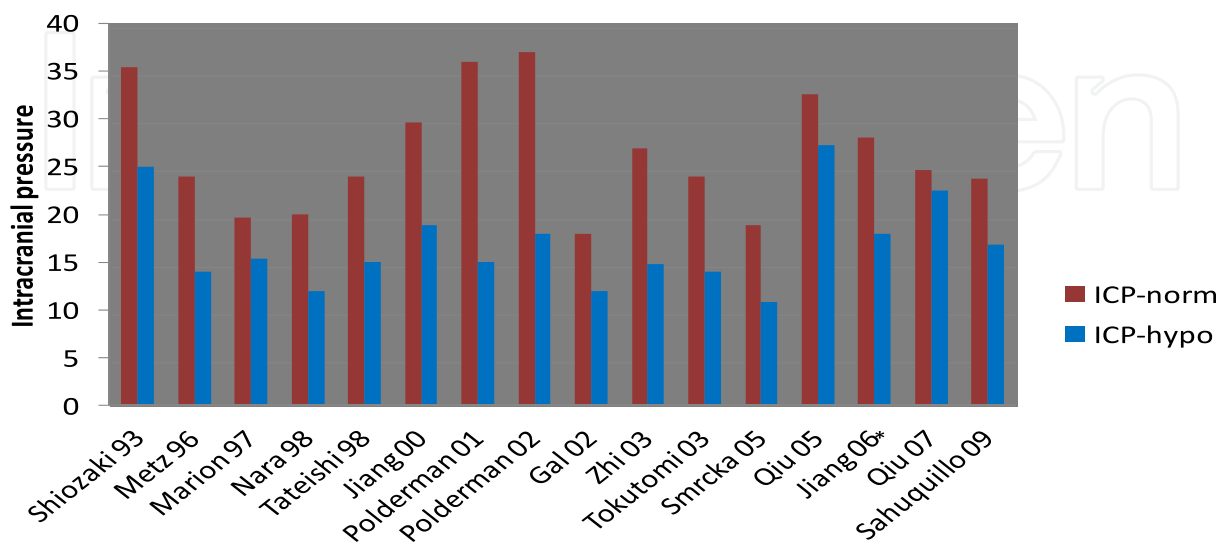
We identified a total of 18 studies involving hypothermia for control of ICP; 13 were randomized clinical trials and 5 were observational studies as shown in tables 1 and 2 respectively [54, 58-74]. In all studies, the patient populations were comprised of TBI patients with GCS < 9 and an abnormal CT scan. ICP monitors were inserted in all patients to measure ICP. Individual study sizes ranged from 9 to 396 patients; a total of 1,773 patients were included in this review. Only three studies were multicenter [54,72,74]. The goals of therapy were stabilization or improvement of the patient's neurological condition, and maintenance of an ICP of 20 mmHg or less (normal value in healthy subjects: ≤ 15 mmHg) and a cerebral perfusion pressure (CPP = MAP - ICP) of 60 mmHg or more or 70 mmHg or more. In patients with ICP higher than 20 mmHg, initial (standard) treatment included appropriate sedatives, narcotics, treatment with neuromuscular blockers (for ICP control and/or shivering) and administration of hyperosmolar therapy. Neurosurgical interventions were undertaken when necessary to evacuate subdural lesions or large intracerebral lesions [58, 61, 63, 64, 66-74]. In nine studies, there was no mention of the use of barbiturates for ICP control [60, 62, 64, 68, 69, 71-74]. In five of the studies, therapeutic hypothermia was applied after elevated ICP failed to respond to adequate sedation, hyperosmolar therapy and barbiturates [58, 63, 65-67]. In the other four studies [54,59, 61,70], patients were randomized to hypothermia or normothermia irrespective of ICP, with the goal of studying hypothermia's role as a neuroprotectant (discussed below). ICP control was looked at as a secondary outcome in these four studies.

Target temperature (32°C – 34 °C) was achieved very quickly in most studies. Therapeutic hypothermia was maintained from 24 hrs up to 14 days depending on the study protocols. Some studies achieved re-warming passively over 10- 24 hrs [67,70, 71,73], but most studies achieved slow active rewarming over 12- 24 hrs as shown in tables 1 and 2. In one study, hypothermia maintenance for five days was associated with less rebound ICH than hypothermia for two days [72]. Therapeutic hypothermia was effective in controlling ICH in all studies as shown in tables 1 and 2 and figure 1. In the 13 RCT, ICP in the therapeutic hypothermia group was always lower than ICP in the normothermia group, and this difference always reached statistical significance as evidenced in table 1 and figure 1. In the 5 observational studies, ICP during hypothermia was always lower than prior to inducing hypothermia; this difference also always reached statistical significance as shown in table 2. Therapeutic hypothermia also improved neurologic outcome and survival in eleven of the studies as can be seen in table 1.

Reference	No. of patients	Length of cooling	ICP(pre)	ICP(Hypo)	Length of rewarming	Outcome	Complications of hypothermia
Metz et al, 1996	10	25 hrs	24	14 (p<0.05)	22 hrs	7 patients (good recovery) 1 patient (severe disability) 2 patients (dead)	Thrombocytopenia, decreased creatinine clearance, pancreatitis
Nara et al, 1998	9	n/a	20	12 (P<0.05)	n/a	3 m good GOS (8/9= 88.8%)	n/a
Tateishi et al, 1998	9	20-118 hrs (mean=68 hrs)	24	15 (p<0.05)	< 1°C/6hrs	Good GOS 7/9	Infection, increase CRP, thrombocytopenia
Tokutomi et al, 2003	31	48 – 72 hrs	24	14 (p<0.0001)	n/a	6m Good GOS (19%) Mortality (48%)	pneumonia
Sahuquillo et al, 2009	24	155 hrs	23.8	16.8 (p<0.001)	1°C/day	6 month Neurologic outcome (Good: 29.2 %, moderate: 8.3 %)	arrythmias

GOS = Glasgow Outcome Score

Table 2. Effects of Hypothermia on intracranial pressure and outcome in patients with severe Traumatic Brain Injury: Nonrandomized Observational Trials



Reference: In Jiang 06, the comparison is between 2 days of hypothermia (red) and 5 days of hypothermia (blue)

Figure 1. Effect of Hypothermia on Intracranial Pressure (ICP).

5.Therapeutic hypothermia as a neuroprotectant

The premise of the use of TH as a neuroprotectant in TBI is based on the fact that early administration of TH could halt the secondary injury processes discussed above, and thus possibly improve outcome. We identified a total of 9 studies where TH is used as a neuroprotectant in TBI, 5 of the studies designed to deliver TH as a neuroprotectant [54-56,61,70], and 4 of the studies designed to deliver TH for neuroprotection and ICP control [48,64,72,73] (Table 3). In all studies, the patient populations were comprised of TBI patients with GCS < 9 and an abnormal CT scan. ICP monitors were inserted in all patients to measure ICP. Individual study sizes ranged from 26 to 392 patients. In the 4 studies designed to deliver hypothermia for ICP control and as a neuroprotectant, ICP in the TH group was always lower than ICP in the normothermia group, and this difference always reached statistical significance. Outcome was better in the hypothermia group in all of these 4 studies.

The 5 Trials designed with early administration of hypothermia for neuroprotection are described as such:

Marion et al in 1997 enrolled 82 patients of ages 16–75 years where patients assigned to hypothermia were cooled to 33°C a mean of 10 hours after injury, kept cool for 24 hours, and rewarmed over 24 hours [61]. At 1 year followup, 38 % of the patients in the hypothermia group and 62% of those in the normothermia group had poor outcomes ($p = 0.05$). The reported effect was exclusively in patients with admission GCS 5–7 [61]. Clifton in 2001 enrolled 392 patients ages 16–65 years with target temperature of 33°C reached by a little more than 8 hours after injury and maintained for 48 hours [54]. Rewarming was started at 48 hours irrespective of ICP, at a rate of 0.5°C every 2 hours. Outcome at 6 months was poor in 57% of patients in both groups. In subgroup analyses, adverse outcome was associated with hypothermia induction in patients older than 45 years of age, and better outcome was associated with maintenance of hypothermia in patients who were already hypothermic ($<35^{\circ}\text{C}$) on admission [54]. In this study, TH was started fairly late and cooling was slow (average time to target temperature >8 h), and there were problems with hypotension, hypovolemia, electrolytes, and hyperglycaemia. Hypotensive episodes lasting for more than 2 h occurred three times more frequently in the hypothermia group than in the control group. Since even very brief episodes of hypotension or hypovolemia can adversely affect outcome in TBI, these problems might have greatly affected the results of this trial. In 2001, Shiozaki et al enrolled 91 patients who did not have elevated ICP in a study comparing the effect of 48 hours of hypothermia with normothermia [55]. There was no difference in outcome, with 53% of patients in the hypothermia group and 51% of patients in the normothermia group having poor outcomes. The incidences of pneumonia, meningitis, thrombocytopenia, leukocytopenia, hypernatremia, hypokalemia, and hyperamylasemia were higher in the hypothermia than in the normothermia group [55]. In 2005, Smrcka et al. reported a study of 72 patients in whom hypothermia maintained for 72 hours was compared to normothermia [70]. There was no difference in outcome between the two groups. However, patients treated with hypothermia with extracerebral hematomas but not diffuse brain injury had a significantly better Glasgow Outcome Score at 6 months than patients treated at normothermia [70]. In 2011, Clifton et al. started hypothermia in transit to or in the emergency department in a study enrolling 97 patients with TBI [56]. Hypothermia was maintained for 48 hours and patients rewarmed at 0.5°C every 2 hours. A protocol of aggressive fluid expansion during rewarming and low dose morphine was used to prevent the hypotension that had complicated use of hypothermia in the group's first study (above). Overall, there was no improvement in outcome at 6 months, but there was a difference in outcomes of patients with diffuse brain injury and those with evacuated hematomas ($p = 0.001$). Fewer patients with evacuated hematomas treated with hypothermia had poor outcomes (hypothermia - 33%, normothermia - 69%, $p = 0.02$), whereas more patients with diffuse brain injury treated with hypothermia had poor outcomes (hypothermia - 70%, normothermia - 50%, $p = 0.09$). Patients treated with hypothermia had a higher number of total episodes of elevated ICP, especially during rewarming [56]. Again, in this study, hypothermia was maintained for a fixed duration of only 48 hrs, and ICP elevations mainly occurred during and after rewarming. In addition, there were deviations from the protocol in this study, for example the decision to advance the interim analysis, and thus the enrollment of a smaller number of patients than planned.

Reference	No. of patients	ICP control	Neuro-protection	Length of cooling	Outcome
Abiki et al,2000	26	yes	yes	3 – 5 days	positive
Jiang et al,2000	87	yes	yes	3-14 days	positive
Jiang et al,2006	215	yes	yes	2 or 5 days	positive
Qui et al, 2007	80	Yes	Yes	4 days	positive
Marion et al,1997	82		Yes	24 hours	positive
Clifton et al,2001	392		Yes	48 hours	No improvement
Shiazaki et al,2001	91		Yes	48 hours	No improvement
Smrcka et al,2005	72		Yes	72 hours	No improvement
Clifton et al,2011	97		Yes	48 hours	No improvement

Table 3. Studies where Therapeutic Hypothermia is used as a neuroprotectant.

6. Side effects of therapeutic hypothermia in TBI

Complications from hypothermia included electrolyte imbalances, increase in incidence of infections, thrombocytopenia, coagulopathy, arrhythmias (especially bradycardia), pancreatitis, and rebound ICH (during re-warming) as presented in tables 1 & 2. Particular consideration should be given to the rate of rewarming. In one extensive review [84], Povlishock et al showed that posttraumatic hypothermia followed by slow rewarming appeared to provide maximal protection in terms of traumatically induced axonal damage, microvascular damage and dysfunction, contusional expansion, intracranial hypertension, and neurocognitive recovery. In contrast, hypothermia followed by rapid rewarming not only reversed the protective effects associated with hypothermic intervention, but exacerbated the traumatically induced pathology and its neurologic consequences. Povlishock's review concluded that the rate of posthypothermic rewarming is an important variable in assuring maximal efficacy following the use of hypothermic intervention. Two meta-analyses [12, 85] as well showed that duration >48 h and slow rewarming were associated with improved outcome.

7. Discussion

Multiple trials, albeit observational or small single center randomized controlled studies, show that mild to moderate hypothermia consistently lowers high ICP in severe TBI patients as shown in figure 1. It is an accepted premise in the care of severe TBI patients that control of ICP improves survival and possibly neurologic outcome. It follows therefore that induced hypothermia in patients with poorly controlled ICP may be a reasonable therapeutic strategy when routine sedation, analgesia and neuromuscular paralysis fail. This benefit would be relevant regardless of any cellular or metabolic neuroprotective effect. Indeed, the additional potential neuroprotective benefits suggest that therapeutic hypothermia if without negative side effects should be implemented as a part of routine ICP control rather than as rescue therapy. It is puzzling why barbiturates with the well-known negative side effects are recommended while hypothermia with its known efficacy in controlling ICH is not. The reasons for this may be the relative inexperience with TH, complexity of TH implementation, concerns for adverse reactions, and the need for sophisticated technology [86,87]. In 2002, studies have indicated that TH with a reduction of body core temperature (T) to 33 °C over 12 to 24 hours has improved survival and neurologic outcome in cardiac arrest patients [88, 89]. A meta-analysis showed that therapeutic hypothermia for cardiac arrest patients was associated with a risk ratio of 1.68 (95% CI, 1.29-2.07) favoring a good neurologic outcome when compared with normothermia [90]. The number needed to treat (NNT) to generate one favorable neurological recovery was 6. Subsequently, the International Liaison Committee on Resuscitation [91] and the American Heart Association [92] recommended the use of TH after sudden cardiac arrest. As a result, intensivists and neurointensivists have become much more familiar with the methodology (following cardiac arrest) so that the process is now familiar. And with appropriate hypothermia protocols, order sets, and education programs, mild hypothermia can be accomplished with very few side effects. It is important to note, however, that there are important differences between short duration hypothermia following cardiac arrest and long term hypothermia in TBI patients with ICH who frequently also have extracranial injuries and extra attention to the above mentioned side effects should be applied. Hypothermia should no longer be viewed as avant guard or dangerous, and we believe that it should take the place of barbiturates as the best modality for refractory ICH. Indeed, there is an argument, pending large scale studies, to consider it an extension of standard treatment. Pending large multicenter, randomized, controlled trials evaluating the effect of hypothermia on ICP control and outcome, the available data suggests that therapeutic hypothermia deserves at least a level II evidence recommendation for the treatment of refractory ICH.

As for trials classified as designed for neuroprotection, although single-center studies were encouraging, multicenter trials with early administration of hypothermia for a defined period of time irrespective of ICP have almost uniformly been negative except maybe for patients undergoing craniotomy for hematoma evacuations. However,

hypothermia was maintained for a fixed duration of only 48 hrs, and ICP elevations mainly occurred during and after rewarming. These results suggest that a period of 48 hours of hypothermia may be too short to have a beneficial effect on outcome. A standardized one size fit all may be inappropriate. The rate of rewarming plays an important role as well as pointed above. The rebound increase in ICP during and after rewarming in these studies and the encouraging outcomes from the randomized studies that induced hypothermia early and continued it throughout the period of ICP point to the realization that individualizing the duration of hypothermia to fit a patient's ICP in future trials may be a better strategy than a predetermined period of hypothermia regardless of ICP. Another important finding is the differential effect of hypothermia in patients with surgical lesions versus those with diffuse injuries. This could be explained by the ability for volume expansion after surgery and thus less rebound ICP during and after rewarming. However, no final answer on this differential effect can be given at this stage, especially with the low number of patients studied so far. As a result, there is no reason to exclude patients with diffuse injury from future trials.

8. Conclusion

Preliminary evidence points to the effectiveness of mild to moderate therapeutic hypothermia in controlling ICH in severe TBI patients. The experience with induced hypothermia in the treatment of post cardiac arrest patients has demonstrated an acceptable safety profile when the modality is applied in specialized units by experienced personell according to a defined protocol. In addition, the above mentioned studies of therapeutic hypothermia in TBI patients show that the adverse effects of hypothermia are reasonable and managable when hypothermia is done in specialized and experienced ICUs. Pending results from large multicenter studies evaluating the effect of therapeutic hypothermia on ICH and outcome, therapeutic hypothermia should be included as a therapeutic option to control ICP in severe TBI patients. The most challenging issue appears to be rebound ICP during re-warming. We suggest that re-warming only be considered if the patient's ICP is stable and <20mmHg for at least 48 hours, and, thereafter implemented at a rate not faster than 0.25°C per hour. As for future of hypothermia as a neuroprotectant in TBI patients irrespective of ICP, Individualizing the duration of hypothermia to fit a patient's ICP in future trials is a better strategy than a predetermined period of hypothermia regardless of ICP. Design of these trials should also consider both the mechanism being tested and the differential effect between patients with evacuated hematomas and those with diffuse brain injury.

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Conflicts of Interest

The authors report no conflicts of interest.

All authors declare that No competing financial interests exist.

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