

# The Management of Traumatic Brain Injury: Is There a Place for Therapeutic Hypothermia?

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## **Current Standards for the management of Traumatic Brain Injury**

The guidelines for the management of severe traumatic brain injury (TBI), were published as a joint project of the Brain Trauma Foundation and the American Association of Neurological Surgeons in 1995 and updated in 2000.<sup>1</sup> Standards were established for intracranial pressure (ICP) monitoring, ventricular CSF drainage and maintenance of adequate arterial oxygenation, with guidelines for sedation, paralysis and seizure prophylaxis. Treatment of ICP >20-25 mmHg and maintaining cerebral perfusion pressure (CPP) at more than 70 mmHg were established as standards.

First tier therapeutic interventions for raised ICP include hyperventilation to a  $P_aCO_2$  between 30-35 mmHg and CSF drainage (Figure 1). Mannitol (0.25-1.0 g/kg) is also recommended for increased ICP. However, to achieve a serum osmolarity of <320 mOsm/l with mannitol therapy while simultaneously trying to maintain euvoemia is clinically difficult. Second tier therapies for persistently elevated ICP include the use of barbiturates and hyperventilation to a  $P_aCO_2$  <30 mmHg (Fig 1). Consideration was given to the use of jugular bulb oxygen saturation ( $S_{jv}O_2$ ) and cerebral blood flow (CBF) monitoring for patients with persistently elevated ICP.

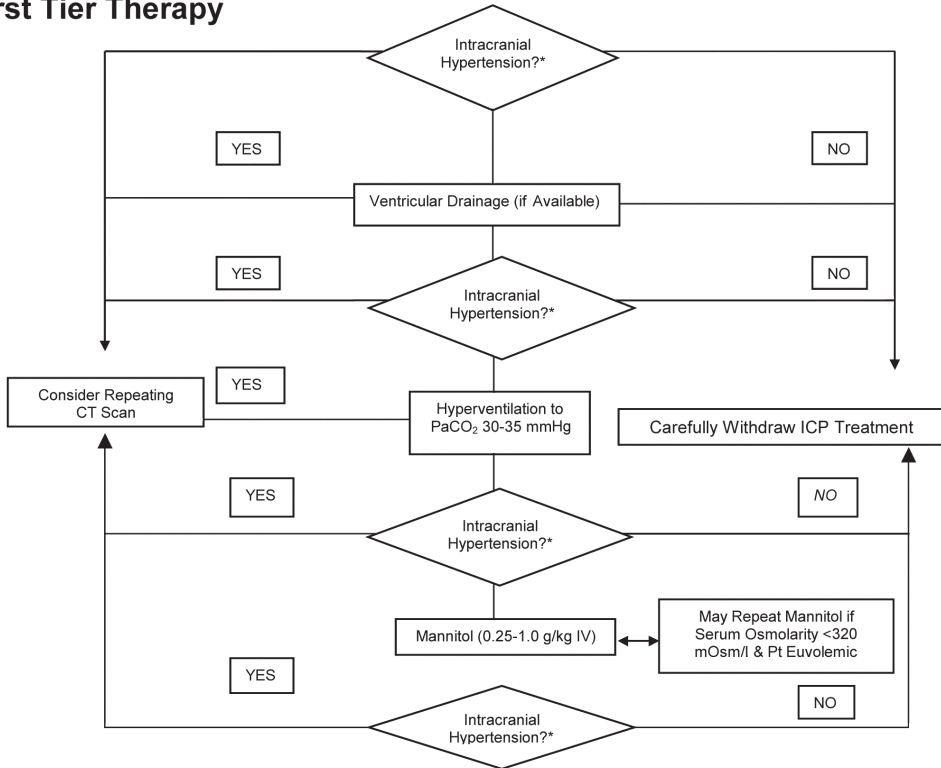
The European Brain Injury Consortium (EBIC) has also established practical guidelines for the management of patients with TBI. The EBIC guidelines emphasise the need for monitoring of ICP,  $S_{jv}O_2$  and EEG (to detect and treat seizure activity and during high dose barbiturate therapy). Recommendations were made for treatment of ICP at or above 20 mmHg, CPP >60 (and preferably >70) mmHg, establishing the absolute threshold for  $P_aCO_2$  not <30 mmHg, maintaining  $SpO_2$  >95% and maintaining arterial haemoglobin level >60 g/l.<sup>2</sup>

These guidelines<sup>1,2</sup> have attracted considerable criticism in the medical literature. Existing trials have not recruited a sufficient number of patients to confirm or refute the existence of a real benefit from the use of hyperventilation, mannitol, CSF drainage, and/or barbiturate therapy.<sup>3,4</sup> A large-scale multi-centre study is currently being undertaken to evaluate the role of corticosteroid therapy after significant TBI.<sup>5</sup>

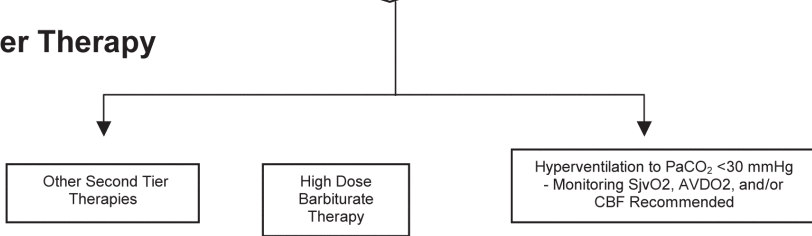
## **Therapeutic Hypothermia for Traumatic Brain Injury?**

The use of therapeutic hypothermia for TBI is the subject of considerable

**First Tier Therapy**



**Second Tier Therapy**



\*Threshold of 20-25 mmHg may be used. Other variable may be substituted in individual conditions

**Figure 1.** First tier therapy.

controversy in the medical literature. Despite several enthusiastic reports,<sup>6,7,8,9</sup> a recent multi-centre trial by Clifton et al,<sup>10</sup> comparing the effects of hypothermia with normothermia among patients with severe TBI reported no clinical benefit. The Clifton study, enrolled 392 patients randomly assigned to be treated, and concluded that treatment with hypothermia, with the body temperature reaching 33°C within 8 hours after injury, is not effective in improving outcomes in patients with severe TBI. The patients in the hypothermia group had more hospital days with complications than the patients in the normothermia group.

### Physiological considerations

Normal young adults, have a morning oral temperature of approximately 36.7°C (SD+0.2°C). Oral temperature in 95% of normal young adults varies between 36.3-37.1°C.<sup>11</sup> The normal core temperature has circadian fluctuations of 0.5-0.7°C and is lowest at 0600 hours. In women, there is in addition a monthly temperature variation characterised by a rise in basal body temperature at the time of ovulation. During anaesthesia and critical care, the body temperature is typically measured at the tympanic membrane, pulmonary artery, nasopharynx, oesophagus, rectum and/or skin. Intracranial temperature can be measured by using an epidural or intra-parenchymal probe. When intracranial temperature is measured using either a ventricular or epidural thermistor, the temperature gradient fluctuates between 0.4-1°C.<sup>12</sup> A temperature gradient of up to 2°C between core temperature and brain temperature has been described.<sup>13</sup>

Hypothermia is defined as a body temperature, below normal in a homeothermic mammal. Hypothermia is classified as:

- Mild: 35-36°C
- Moderate: 32-34°C
- Severe: <32°C

### Historical perspectives

Aristotle said that the brain was an organ for cooling the blood.<sup>14</sup> Of course, the brain does cool or warm the blood and the body quite efficiently in the course of its operations. Hypothalamic reflexes initiated by cold cause shivering. Reflex responses activated by warmth are primarily controlled from the anterior hypothalamus, which triggers cutaneous vasodilatation and sweating. The signals which activate the hypothalamic temperature regulating centres come from two sources: temperature sensitive cells in the anterior hypothalamus and cutaneous cold receptors.

Hippocrates advocated snow and ice to check haemorrhage and was aware of the analgesic effects of cold. Baron Larrey, a surgeon in Napoleon's army, also became aware of the therapeutic effects of hypothermia in soldiers who had undergone painless amputation of limbs. Refrigeration anaesthesia was first described in 1866.<sup>15</sup>

Modern interest in the use of therapeutic hypothermia began in 1938-1940, with the reports by Smith and Fay<sup>16</sup> from the Temple University School of Medicine in Philadelphia. These researchers reported that treatment of human cancers with locally applied cooling to reduce temperatures to 75-90°F arrested tumour growth. These authors observed that a reduction in temperature induced physiologic changes in tumour cells that were comparable to those induced by irradiation therapy, i.e. nuclear destruction and cytoplasmic disintegration. Smith and Fay also noted the adverse effects of hypothermia on renal function, blood chemistry, and basal metabolic rate. They advised that medical personnel should only attempt the use of therapeutic hypothermia for cancer therapy in medical institutions with the capability of monitoring an individual patient's clinical course. They emphasised the benefit of low temperatures in producing pain control when applied to tissue compartments. Smith and Fay concluded that: "its (therapeutic hypothermia) usefulness in the therapeutic field otherwise remains a problem to be solved in the future". In a subsequent report, Fay<sup>17</sup> described his earlier experiences of localised and generalised refrigeration of the human brain to control a variety of clinical conditions including cancer, leukaemia, glioblastoma, Hodgkins Disease, filariasis, and syphilis.

The horrors of human experimentation, including the use of hypothermia, in the Nazi concentration camps between 1939 and 1945 were highlighted in the Nuremberg Trial and in Lifton's publication titled "Medical Killing and the psychology of genocide".<sup>18</sup>

### **Patho-physiological rationale for the use of therapeutic hypothermia**

Hypothermia reduces intracranial pressure, increases cerebral perfusion pressure, lowers the cerebral metabolic rate, and reduces the cerebral spinal fluid concentration of interleukin-1 $\beta$  and glutamate. Mechanisms by which therapeutic hypothermia may be beneficial in, at least, sub-groups of patients with TBI include a significant reduction in excitatory amino acids during the period of cooling and sustained suppression of cytokines, particularly interleukin-1 $\beta$ . Stabilisation of the blood brain barrier and a general reduction in the post-traumatic hypermetabolic state also occur.

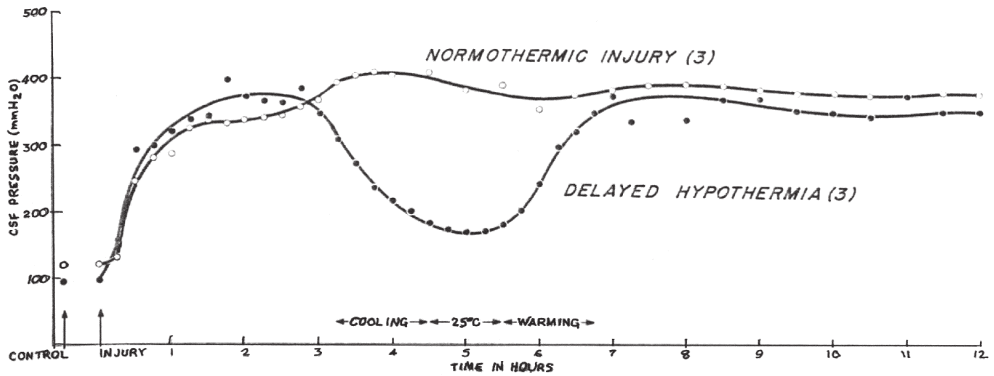
### **Statistical Criticisms**

Despite these patho-physiological considerations, Hartung and Cottrell<sup>19</sup> made critical editorial comments regarding the lack of useful data to support the use of hypothermia in patients with TBI. Both these authors provide powerful insights into the methodologies and statistical analytical methods which were employed in the clinical trials for the use of therapeutic hypothermia for TBI. This critique, highlights the importance of sample size calculations in clinical studies; the role of inadvertent bias and perhaps inadvertent misinterpretations of *P* value probability differences. The authors conclude that: "Only regression and co-variant analyses address such differences statistically, referring to *p* values which are intended to serve the purpose of highlighting important differences from differences that should be dismissed, and then only when the study sample size is sufficiently large to make them meaningful."

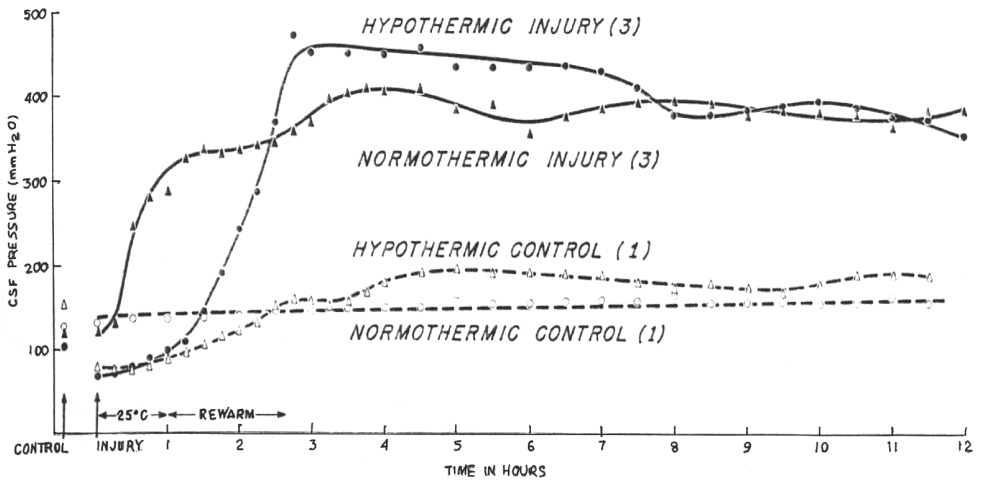
### **Experimental studies in Brain Injury**

In 1950, Bigelow et al first described hypothermic protection following cerebral ischaemia in dogs after total cardiac arrest for 15 minutes.<sup>20</sup> A comprehensive review of Phase I and Phase II animal studies supporting the use of therapeutic hypothermia in the treatment of severe TBI can be found in a review by Clifton and Hayes.<sup>21</sup> In the study on dogs by Rosomoff et al<sup>22,23</sup> hypothermia was induced by immersion up to the shoulders in ice water. Rewarming was achieved by immersion in a water bath in which the temperature was maintained 10°C higher than body temperature until normothermic levels were reached. The CSF pressure measurements in the four groups of animals plotted against time are shown in Figures 2 and 3. In this study, it was demonstrated that application and maintenance of reduced body temperature clearly changed the pathologic character of experimental brain injury. Hypothermia prevented the development of progressive fulminating brain oedema associated with injuries at normal body temperature. Hypothermia also altered the post-traumatic inflammatory cellular response. Despite these beneficial effects, all the animals died when they were rewarmed. Their survival times were, however, five times longer than the normothermic controls.

In the study, the CSF pressure following injury was noted to rise slowly after the first hour to a peak by about the fourth hour, whereupon it remained relatively stable for up to twelve hours. Quite paradoxically, CSF pressure measurements did not reflect the continuing sizeable increase in brain volume due to cerebral oedema that occurred



**Figure 2.** Cerebrospinal fluid pressure after brain injury at normal body temperature and with CSF Pressure after TBI at normothermia and during delayed hypothermia. Redrawn from data in the original publication.



**Figure 3.** CSF Pressure at normothermia and hypothermia, with standard brain injuries and controls. Redrawn from the data in the original publication.

between the fourth and twelfth hour. Furthermore, there was no correlation between the level of CSF pressure and mortality. It was noted that the CSF pressure was reduced during the induction and maintenance of hypothermia in these experiments. With rewarming, the pressure reverted to levels established for normothermic controls, seemingly affected only temporarily by the reduction in temperature. This suggested that the CSF pressure alone is not an indication of prognosis, since there was no correlation between CSF pressure measurements and mortality.

In a similar study by Civalero et al<sup>24</sup> on dogs, the temperature in various organs was recorded during internal cooling. The true brain temperature was higher during cooling than the mean recorded temperature in other organs of the body. Brain

temperature was found to be 8-10°C (up to max of 14°C) above the recorded oesophageal temperature. In addition, the oxygen consumption during rewarming was greater than prior to cooling when the temperature was 37°C. These experimental observations are not only important but are also physiologically consistent with the hypothalamic thermoregulatory response increasing its neuro-humoural output in an attempt to re-establish normothermia.<sup>25</sup>

Earlier animal studies showed a reduction in the rate of cerebral oedema formation and mortality after injury to the cerebral cortex.<sup>26</sup>

### **Adverse effects of hypothermia**

Therapeutic hypothermia can be associated with significant adverse effects.<sup>27</sup>

#### *CNS*

Hypothermia results in progressive reduction of neuronal function, which may manifest as confusion, disorientation, stupor and coma. This reduction results in changes in electrophysiological monitoring. The EEG shifts to slower frequencies while the somatosensory evoked potentials (SSEP) shows prolongation of latencies and a reduction in amplitude.

#### *Respiratory, Shivering and Oxygen Consumption*

Hypothermia causes a transient increase in ventilation before the more characteristic depression. Both respiratory rate and tidal volume are reduced; this appears to be due to a central CNS effect. Experimentally selective rewarming of the brain stem reverses these respiratory effects. Shivering is the most widely recognised side effect of hypothermia. More recent carefully controlled studies suggest that total body oxygen consumption increases by 40-100% during shivering. Such increases in oxygen consumption could have adverse effects on organs such as the heart or the brain, that may have fixed vascular obstructions to the arterial blood flow.

#### *Cardiovascular System*

Hypothermia results in a substantial activation of the sympathetic nervous system as is evident by an increase in circulating noradrenaline and associated vasoconstriction. The sympathetic effects may cause myocardial ischaemia both through peripheral and coronary vasoconstriction. The cardiac conduction system is cold sensitive and hypothermia causes bradycardia, prolonged PR intervals, widening of the QRS complex and prolongation of the QT interval resulting in the typical "J-wave". Atrial fibrillation is common below 32°C.

#### *Renal*

There is progressive depression of renal tubular function with a marked reduction in the tubular reabsorptive capacity that results in "cold diuresis". Sympathetic neuronal stimulation with cutaneous and splanchnic vasoconstriction also contributes to diuresis.

#### *Immune System and Infection*

Experimentally induced hypothermia reduces the function of neutrophils, lymphocytes, and macrophages. This has been shown to be associated with a high incidence of wound infections and pneumonia.

*Haematological effects*

There is an increase in blood viscosity and a marked defect in coagulation parameters and platelet function that results in increased bleeding diathesis.

*Altered Pharmacokinetics and Pharmacodynamics*

Hypothermia potentiates the effects of central nervous system depressants and prolongs the duration of action of drugs dependent on enzymatic systems for their clearance, eg the duration of action of non-depolarising neuromuscular blockers is prolonged.

*Electrolyte abnormalities*

Hypophosphataemia, hypomagnesaemia, hyper- and hypo-calcaemia, and other electrolyte abnormalities have been reported during therapeutic hypothermia.<sup>28</sup>

**Hyperthermia in patients with TBI**

Fever is common in critically ill patients with neurotrauma, especially those patients with a prolonged length of stay in the ICU. Hyperthermia is associated with adverse outcomes in patients with TBI. It is therefore common practice for body temperature to be reduced using antipyretic medications (paracetamol) and external body cooling when the body temperature is elevated beyond 38.5°C in these patients, at least so as to maintain normothermia.<sup>29</sup>

**Ethical Considerations**

In his editorial discussing the multi-centre randomised study by Clifton et al,<sup>10</sup> Narayan<sup>30</sup> considers why so much laboratory and earlier clinical data struck an “optimistic note in favour of therapeutic hypothermia”, while the Clifton study revealed no benefits. He noted that 38% of the patients involved in this study were enrolled without consent. Arguments in favour of consent waiver included the inability of severely head injured patients to consent themselves and relatives being unavailable within the short timeframe (less than 6 hours) required to institute treatment.

It can be ethically argued that further studies are required, with the consent of relatives or next-of-kin, to identify categories of patients who would benefit from the use of therapeutic hypothermia in traumatic brain injury. Does a single negative study mean that therapeutic hypothermia should not be used clinically? Perhaps not. The Clifton study found that hypothermia may be beneficial in a certain proportion of patients below the age of 45 years, with intractable high ICP. Two separate non-randomised studies by Jiang<sup>8</sup> and Shiozaki<sup>9</sup> support this observation.

Therapeutic hypothermia for TBI cannot be regarded as standard treatment and protocols for its use must incorporate the uncertainties associated with its routine application. Enthusiastic clinicians, who wish to institute therapeutic hypothermia for severe TBI as a life-saving measure, should obtain informed consent from a responsible person on behalf of the patient. The Informed Consent information sheet and the treating clinician should clearly explain that therapeutic hypothermia is a life-threatening intervention used in an attempt to save the patient's life, despite the fact that a medical publication has failed to confirm the benefit in a clinical trial. Such Informed Consent procedures would provide safeguards for clinicians and institutions against clinical and legal criticisms if, and when, the patient develops disabilities or death, which may be attributable to the therapeutic hypothermia. Conservative

clinicians must await further studies to determine the sub-population of patients most likely to benefit from the treatment.

### Future considerations

Any future studies must specify the population of patients to be studied and to compare them with standard guideline directed treatments as control. Further, it would be necessary to define the duration and the extent of the therapeutic hypothermia, the target starting and definitive temperature endpoints. New protocols should be produced with firm indications and exclusions for its use. The treatment time frame must be specified and a rigorous schedule for cooling and rewarming (duration of hypothermia treatment and target rate of rise of temperature). Since this treatment cannot be administered in a double blind fashion, enthusiasm for its use should be tempered by conservative analysis. Protocols must have a clear understanding of the outcomes and serious adverse events, including death, must be recorded and published. The study must enrol a sufficiently large number of patients to detect the possibility of a statistically significant difference in treatment.

The reader is reminded that this critique pertains to the use of therapeutic hypothermia for TBI. This review specifically excludes analysis of the publications on the use of therapeutic hypothermia in other clinical circumstances during anaesthesia, resuscitation and critical care.

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