

# Hypothermia Improves Outcome From Traumatic Brain Injury

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## ABSTRACT

*Hypothermia for patients with severe traumatic brain injury (TBI) remains controversial despite a strong biological rationale and reasonable evidence from the literature. The “negative” Clifton study seems to have reduced enthusiasm for hypothermia, however the aim of this review is to analyse the evidence from all randomised controlled trials (RCT) and meta-analyses on this topic to determine whether there is adequate support for the view that hypothermia does improve outcome from TBI.*

*The biological rationale for hypothermia is supported by animal and human mechanistic studies of TBI and human clinical studies of brain injury caused by out-of-hospital cardiac arrest. Several small single-centre RCT’s have demonstrated that hypothermia leads to both improved survival and improved favourable neurological outcome in TBI. The Clifton study, which was larger and multi-centre, found hypothermia had no major benefits in TBI, although this study can be criticised for several issues of trial methodology (trial design and application of the intervention) and group comparison. Several meta-analyses have given slightly discordant results, but the two most recent meta-analyses agree that hypothermia improves favourable neurological outcome and probably survival. Subsequent to these meta-analyses, a RCT was published which has confirmed that hypothermia is beneficial in a large group of TBI patients. When the published evidence is considered in total, even if hypothermia can’t be justified in all TBI patients, if it is applied optimally in the most appropriate patients, hypothermia certainly improves outcome from TBI.*

*If hypothermia is correctly applied (early, long and cool enough) in the optimal group of TBI patients (young with elevated ICP), there seems to be no doubt that hypothermia is effective in improving both survival and favourable neurological outcome from TBI. (Critical Care and Resuscitation 2005; 7: 238-243)*

**Key words:** Traumatic brain injury, therapeutic hypothermia, review

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The induction of hypothermia as a strategy in the management of patients with severe traumatic brain injury (TBI) has attracted significant controversy over the last decade despite a strong biological rationale and reasonably solid evidence from the literature. Enthusiasm peaked around the year 2000 after the publication of several small single-centre randomised controlled trials (RCT),<sup>1-4</sup> all of which showed that hypothermia improved neurological outcome in TBI patients. However the results of a “negative” moderate-sized multi-centre RCT<sup>5</sup> halted momentum significantly and the publication of several meta-analyses has fuelled the controversy, reflected by the results of a 2003 survey which revealed that a moderate number (41%) of United

Kingdom ICU’s use hypothermia for TBI patients.<sup>6</sup>

It is timely to debate this issue. Because the consequences of TBI can be so devastating to individuals, their families and our community, it is important that clinicians thoroughly understand the role of all possibly therapeutic interventions.

The objective of this review is to argue that the purposeful induction of hypothermia for patients with TBI *does* improve outcomes, by reviewing the biologic rationale as well as the published evidence from RCT’s and meta-analyses.

## Biological rationale

There can be little doubt that there is a strong biolo-

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gical rationale for the use of hypothermia (which is generally defined as the lowering of body temperature to between 32 and 35 degrees Celsius (°C)) in patients with TBI. Animal studies have demonstrated that (1) hypothermia improves survival after TBI,<sup>7</sup> and that (2) hypothermia modulates many of the immunological, cerebral metabolic and other biochemical pathways involved in secondary brain injury.<sup>8,9</sup> This rationale is supported by the fact that hypothermia improves neurological outcome and survival in patients following out-of-hospital cardiac arrest, a brain injury which has many similarities to TBI.<sup>10,11</sup>

In clinical studies of patients with TBI, hypothermia reduces intracranial pressure (ICP),<sup>2-4,12</sup> reduces cerebral metabolic rate (without a reduction in cerebral blood flow),<sup>13</sup> reduces serum lactate<sup>12</sup> and increases both brain tissue and jugular vein oxygenation.<sup>12</sup> But whether hypothermia affects clinically-meaningful outcomes in TBI patients is a more important question.

### Clinical studies prior to 2001

Hypothermia first came into mainstream clinical practice following 2 studies published in 1993. The first of these (which was designed as a Phase II study) randomly assigned 46 severe TBI patients to hypothermia (32 - 33°C) or normothermia (37°C), and found that hypothermia led to significantly fewer seizures but it also led to non-significant increases in the number of patients who went on to have a favourable neurological outcome (on the one hand) but also to develop sepsis (on the other hand).<sup>1</sup> The second study randomised 33 severe TBI patients (who also had persistent ICP > 20 mmHg) to hypothermia (34°C) or normothermia and found that hypothermia led to significantly lower ICP, higher cerebral perfusion pressure (CPP) and improved survival (50% versus 18%;  $p < 0.05$ ) than normothermia.<sup>2</sup>

A third study (which had released preliminary results previously<sup>14</sup>) randomised 82 patients with severe TBI to either hypothermia (32 - 33°C) or normothermia (37 - 38.5°C). Hypothermia significantly reduced ICP, increased CPP and was associated with an improved incidence of favourable neurological outcomes at 3 (38% versus 17%;  $p = 0.03$ ) and 12 months (62% versus 38%;  $p = 0.05$ ) after injury. Subgroup analysis showed that patients with a Glasgow Coma Scale score (GCS) of 3 - 4 at presentation did not benefit from hypothermia whilst those with a GCS of 5 - 7 did.<sup>3</sup>

A subsequent RCT enrolled 87 patients and found that hypothermia reduced mortality (26% versus 46%;  $p < 0.05$ ) and improved favourable outcomes (47% versus 27%;  $p < 0.05$ ) at 12 months after injury when compared to normothermia. This study used hypo-

thermia (33 - 35°C) for between 3 and 14 days until ICP was below 15 mmHg.<sup>4</sup>

Around the same time, a Japanese group performed a multi-centre study of 91 TBI patients with controlled ICP (< 25 mmHg) to assess whether these presumably less severely injured patients would benefit. The hypothermia (34°C) group and the normothermia (37°C) group had similar neurological outcome and survival rates, but the hypothermic group had significantly higher rates of pneumonia and meningitis, as well as various haematological and biochemical abnormalities (including leukocytopenia, thrombocytopenia, hypernatraemia, hypokalaemia and hyperamylasaemia).<sup>15</sup>

The literature up until 2001 could therefore have been summarised by claiming that hypothermia improved neurological function and survival in TBI patients overall (but that it was unlikely to have been of any benefit in patients with stable ICP or GCS 3 - 4).

### The multi-centre Clifton study published in 2001

In 2001 a multi-centre study from the USA was published which had enrolled 392 patients and randomised half to be cooled to 33°C (within 8 hours) and half to receive normothermia.<sup>5</sup> Hypothermia led to a reduced incidence of intracranial hypertension (episodes of ICP > 30 mmHg) but to similar rates of poor neurological outcome (57% versus 57%;  $p = 0.99$ ) and death (28% versus 27%;  $p = 0.79$ ) when compared to normothermia. In subgroup analysis, hypothermia led to more poor neurological outcomes in patients > 45 years of age and led to better outcomes in those patients < 45 years who were hypothermic on enrolment into the study.

This study was significantly larger than previous studies, was multi-centre and was generally methodologically sound, however there are a number of points worth considering in light of the fact that hypothermia was found not to influence neurological function and survival:

1. The majority of patients (88%) were enrolled from a minority of study centres (5 of 11 centres) and there was significant inter-centre variance between centres participating in this study.<sup>16</sup> Such variance in protocol adherence and application of hypothermia may well have introduced an unrecognised bias.
2. Whilst the study involved many patients with intracranial hypertension, a high ICP was not a condition of entry into the trial. Because a Japanese study showed a lack of benefit when hypothermia was used in TBI patients with controlled ICP,<sup>15</sup> this may have contributed to enrolling many patients who would have been unlikely to have benefited from the intervention.

3. By excluding patients with hypotension and hypoxaemia after resuscitation, the study may have excluded patients with more severe TBI, who may have been the most likely to have benefited from the intervention.
4. Because the average randomisation time after injury was close to 4 hours with an aim to reach the desired temperature by 8 hours, it is plausible that the intervention was applied too late to have had an effect.
5. Muscle relaxants (namely vecuronium) were used for the induction of hypothermia and also as the first line treatment for raised ICP. Perhaps surprisingly the mean vecuronium dose was higher in the normothermic arm, however because exposure to muscle relaxants is potentially harmful in TBI patients,<sup>17</sup> the actual number of patients who received vecuronium in each group should have been reported.
6. Active rewarming of patients occurred after 48 hours irrespective of ICP level. Ceasing hypothermic treatment when ICP was presumably elevated in many patients is counter-intuitive, a view that is supported by the RCT which demonstrated that continuing hypothermia until ICP was below 15 mmHg led to significantly improved outcomes.<sup>4</sup>
7. Despite the randomisation process, minor imbalances in the matching of the groups (there were trends towards more patients with lower GCS in the hypothermia group and more patients with prehospital hypoxaemia in the normothermia group) may have influenced the study results.
8. During the intervention period the hypothermia group received larger doses of vasopressors (for a longer time period), received more intravenous fluid, developed more critical hypotension, developed more complications and had higher daily therapeutic intervention scores, all of which suggest that due to either more severe disease or more severe physiological insult caused by the intervention, the hypothermia group may have been more likely to have had poor outcomes, thereby diluting any benefit hypothermia may have derived.
9. The fact that there were more patients in the hypothermic group with hypothermia at enrolment (who were found to have worsened outcomes in a retrospective analysis described in the manuscript) may have introduced a bias against induced hypothermia.

#### Meta-analyses

There have now been four meta-analyses performed to determine the effects of hypothermia on various outcomes in TBI patients. The first, published in 2002, aggregated 7 studies (involving 668 patients) and found

that hypothermia led to a small and non-significant reduction in ICP (weighted mean difference (WMD) - 2.98 mmHg; 95% confidence interval (CI) -7.58 - 1.61, had no significant effect on favourable neurological outcome (odds ratio (OR) 0.61; 95% CI 0.26 - 1.46), had no significant effect on development of pneumonia (OR 2.05; 95% CI 0.79 - 5.32), had no significant effect on development of cardiac arrhythmia (OR 1.27; 95% CI 0.38 - 4.25) but led to a small and significant increase in partial thromboplastin time (WMD 2.22 seconds; 95% CI 1.73 - 2.71).<sup>18</sup>

In 2003, 8 studies of 748 patients were aggregated and hypothermia was found to have had no significant effect on mortality (OR 0.81; 95% CI 0.59 - 1.13), and an almost significant reduction in unfavourable neurological outcomes (OR 0.75; 95% CI 0.56 - 1.01), but at the expense of a significantly increased rate of pneumonia (OR for normothermia developing pneumonia 0.42; 95% CI 0.25 - 0.70).<sup>19</sup>

A subsequent 2003 meta-analysis was larger and aggregated 12 studies with 1069 patients.<sup>20</sup> Hypothermia reduced mortality significantly (relative risk (RR) 0.81; 95% CI 0.69 - 0.96), and in focussing on measures that strengthen this association, there was no significant methodological heterogeneity between studies and no suggestion of publication bias (using funnel plot testing). Hypothermia also reduced the risk of poor neurological outcome significantly (RR 0.78; 95% CI 0.63 - 0.98). This meta-analysis also examined the duration and depth of hypothermia and found that hypothermia for > 48 hours had lower risk ratios for mortality (RR 0.70; 95% CI 0.56 - 0.87) and poor neurological outcome (RR 0.65; 95% CI 0.48 - 0.89), whilst hypothermia to 32 - 33°C reduced the risk of poor neurological outcome even further (RR 0.61; 95% CI 0.45 - 0.83).

Finally, a Cochrane review published on the world wide web in 2004 aggregated 14 trials with 1094 patients.<sup>21</sup> Hypothermia significantly reduced long-term unfavourable neurological outcomes (OR 0.75; 95% CI 0.56 - 1.00), almost significantly reduced mortality (OR 0.80; 95% CI 0.61 - 1.04) but significantly increased the risk of pneumonia (OR 1.95; 95% CI 1.18 - 3.23). These results did not include the study of hypothermia that was defined to be "deferred" (when other interventions for refractory intracranial hypertension had been tried) which was analysed individually.<sup>2</sup> This study had a substantial effect on reduction of poor neurological outcomes (OR 0.10; 95% CI 0.01 - 1.00) and a large but non-significant effect on 6 month mortality (OR 0.21; 95% CI 0.04 - 1.05).

It is somewhat difficult to rationalise the slightly discordant results of these meta-analyses (given they were all published over a 2 year period) however the 2

more recent meta-analyses concurred that hypothermia increases the chance of a favourable neurological outcome. In addition it is highly likely that hypothermia increases survival despite a definite increased risk of pneumonia and a slightly higher partial thromboplastin time.

#### **A more recent large RCT**

The largest RCT in this field was published recently by a group of Chinese investigators.<sup>12</sup> This study enrolled 396 severe TBI patients at a single institution and randomly assigned 198 patients to hypothermia (32 - 35°C) and 198 to normothermia (36.5 - 37°C). The hypothermia (which was induced within an average of 9 hours of injury and continued for an average of 62 hours) significantly reduced ICP (by as much as 7 mmHg on the 3<sup>rd</sup> day), significantly reduced mortality (26% versus 36%;  $p < 0.05$ ) and significantly increased favourable neurological outcomes (39% versus 20%;  $p < 0.05$ ). The hypothermia was continued until the ICP was stable for 24 hours and rewarming occurred over 16 to 20 hours.

This study had similarities to the Clifton study with respect to size (approximately 400 patients each), time until hypothermia goals were reached (8 - 9 hours) and patient eligibility criteria (enrolment of patients with GCS 3 - 8, no absolute requirement for elevated ICP and exclusion of hypotensive patients after resuscitation).

The predominant difference between the 2 studies, which may have explained the profound difference in outcome of the studies, was the duration of hypothermia. In this Chinese study, hypothermia was applied for longer than in the Clifton study (62 versus 48 hours) but the discontinuation was guided by ICP stability (whereas the Clifton study did this at 48 hours regardless of the ICP).

The drawbacks of this Chinese study are that it was performed in a single institution and the published report provided almost no detail about whether baseline equivalence of the study arms occurred as well as little information regarding co-interventions and complications of the intervention.

#### **Summary of current evidence from RCT's and meta-analysis**

When all of this evidence is summarised, it seems reasonable to contend that TBI patients who are actively cooled have a significantly greater chance of a favourable neurological outcome, as the largest RCT<sup>12</sup> and the 2 most recent meta-analyses<sup>20 21</sup> (aggregating studies of over 1000 patients) all concur on this fact. Whether it is possible to make the claim that hypothermia increases overall survival is not immed-

ately as clear-cut, because whilst the Chinese RCT did show this<sup>12</sup>), 1 of the 2 most recent meta-analyses found a significant difference<sup>20</sup> and the other found only a trend in this direction.<sup>21</sup> Given that both of these meta-analyses did not include this most recent and largest RCT,<sup>22</sup> the addition of this result would almost certainly reduce the width of the confidence intervals to such an extent that a significant improvement in survival would be demonstrated.

Whilst the results of the Clifton study feature strongly in any argument against hypothermia in TBI,<sup>5</sup> it must be remembered that there are many plausible reasons why this study may have led to contradictory findings, including the view that a RCT can be "negative" due to chance itself.

Given that many clinicians remain unconvinced by the cumulative evidence regarding hypothermia in TBI patients<sup>6</sup>, review of the results of the hypothermia studies leads to the view that even if hypothermia can't be justified in all TBI patients, a strong case can be made that if hypothermia is applied optimally (early enough, long enough and cool enough) in the most appropriate TBI patients (with elevated ICP, younger in age), there is no doubt that it will improve outcomes.

#### **Hypothermia induced early enough**

Two of the RCT's demonstrating outcome benefits in favour of hypothermia in TBI began cooling almost immediately<sup>3,4</sup> and many of the studies demonstrating the effectiveness of hypothermia in animal models of TBI began the therapy in the first 60 - 120 minutes after injury. Given also that human studies where hypothermia was shown to improve outcome after cardiac arrest began cooling within 2 hours,<sup>10,11</sup> patients in both clinical practice and future trials should have all attempts made to achieve the minimum desired temperature within the first 4 hours at the latest. Use of intravenous cooling may be a more expedient method to achieve this aim.<sup>22</sup>

#### **Hypothermia induced for long enough**

Hypothermia should be applied for at least 48 hours and should be guided by ICP given that this has been the common feature of the RCT's where hypothermia has been most effective in patients with TBI.<sup>2,4,12</sup> Support for this view also comes from the sub-group results of the meta-analysis that demonstrated hypothermia for > 48 hours was associated with a lower relative risk ratio and tighter confidence intervals than other time periods for mortality.<sup>20</sup> Cessation of hypothermia at a specific time point prior to control of ICP is therefore ill-advised and has been appropriately likened to extubating a patient with pneumonia prior to resolution of respiratory failure.<sup>23</sup>

### Cool enough hypothermia

The actual body temperature that should be targeted when inducing hypothermia remains more controversial than some other aspects of the therapy. A meta-analysis concluded that cooler temperatures were more beneficial,<sup>20</sup> however the largest and most recent study with an outcome benefit used a wide aim of 32 to 35°C,<sup>12</sup> when other studies have had more narrow approaches. Given that the risk of side effects seems to be greater with lower temperatures,<sup>24</sup> more research is required to determine the optimal temperature.

### Most appropriate TBI patients

One RCT specifically focussed on TBI patients with low ICP and concluded that hypothermia did not improve outcomes in this group.<sup>15</sup> In addition, there may be concern in cooling patients aged over 45 years based on the sub-group results of the Clifton study.<sup>5</sup> It therefore seems most appropriate that if hypothermia is to be applied in clinical practice that it is more likely to be of value in younger TBI patients with elevated ICP.

### Conclusions

Controversy about hypothermia in TBI patients continues despite the large number of trials performed in this area. Whilst the onus is clearly on clinicians to determine whether hypothermia is both safe and effective, the question arises whether the results of a single trial which perhaps did not apply the intervention adequately, should be the predominant reason not to provide hypothermia. In light of a significant body of evidence from RCT's and meta-analyses, if hypothermia is correctly applied (early, long and cool enough) in the right group of TBI patients (young with elevated ICP), there seems to be no doubt that it is effective in improving both survival and favourable neurological outcome.

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