

Hypothermia Does Not Improve Outcome From Traumatic Brain Injury

I. SEPPELT

Department of Intensive Care Medicine, University of Sydney, Nepean Hospital, Sydney, NEW SOUTH WALES

ABSTRACT

Therapeutic hypothermia is a potentially dangerous treatment with a very narrow therapeutic index. It is of proven benefit in certain conditions, including post ventricular fibrillation cardiac arrest and intermediate severity neonatal asphyxia. It is of no benefit and may cause harm in other contexts, such as elective neurovascular surgery. In traumatic brain injury there has been much provocative early evidence. While it is clear that hypothermia decreases intracranial pressure, a major phase III trial demonstrated no improvement in neurological outcomes with hypothermia, in an unselected group of patient with severe head injury. More focused phase III trials are underway but until the results are known this treatment should not be offered to patients outside the context of a clinical trial. (Critical Care and Resuscitation 2005; 7: 233-237)

Key words: Traumatic brain injury, therapeutic hypothermia, review

Therapeutic hypothermia was first described by Temple Fay in 1940, in a case series of traumatic brain injury (TBI) with a remarkable 100% survival.¹ In 1950 Bigelow *et al*,² reported that the safe cerebral ischaemic time in dogs could be extended to 15 minutes with 20°C hypothermia. The technique was developed in humans in the 1950s and 1960s.³ As well as brain injury, deep hypothermia and circulatory arrest was used for congenital heart disease surgery and complex neurovascular surgery. General use in cardiac surgery was associated with significant side effects and with the advent of good cardiopulmonary bypass the technique was abandoned outside particular paediatric applications. The use of hypothermia for traumatic brain injury was *ad hoc* and overall 121 patients with brain injury were reported in the literature as having been treated with hypothermia between 1958 and 1989.⁴ Due to difficulties and complications the initial flurry of enthusiasm for hypothermia waned, and other therapies particularly barbiturates were trialled for cerebral protection.

Initially it was thought there was a linear relationship between temperature and the cerebral metabolic requirement for oxygen (CMRO₂) with the result that most early reports of hypothermia were with temperatures below 30°C. In 1987 Busto and colleagues⁵ reported that small differences in ischaemic brain temperature were highly protective during global ischaemia, and many laboratories duplicated these findings. It therefore appeared that much more moderate hypothermia might be effective without the significant complications of more profound hypothermia.

Mechanisms

The mechanism by which hypothermia might be neuroprotective remains unclear. Possibilities include reduced basal cerebral metabolism, inhibition of caspase activation leading to neuronal apoptosis, reduced calpain mediated proteolysis, reduced mitochondrial dysfunction, reduced production and release of the excitatory amino acids (especially glutamate) during

Correspondence to: Dr I. Seppelt, Department of Intensive Care Medicine, Nepean Hospital, PO Box 63 Penrith, New South Wales 2751 (e-mail: seppelt@med.usyd.edu.au)

ischaemia, reduced activation of inflammatory mediators such as IL-8 [though IL-6 activation is neuroprotective], reduced free radical production, and reduced vascular permeability of the blood brain barrier leading to vasogenic oedema. Overall the intention is to reduce or delay the consequences of the reperfusion injury.

The risks of hypothermia

A significant number of complications are seen with induced hypothermia. The most common is sepsis, particularly nosocomial pneumonia. In elective surgery accidental hypothermia is associated with delayed wound healing, wound infections and prolonged hospitalisation.⁶ Cardiac arrhythmias are frequent, particularly with core temperatures below 30°C. Arrhythmias are associated with hypokalaemia, hypomagnesaemia, hypocalcaemia and hypophosphataemia in TBI.⁷ Electrolyte abnormalities can also be associated with impaired myocardial contractility. Coagulopathy is well described,⁸ though it appears to be of most significance in multi-system trauma. The so called 'lethal triad' in trauma is hypothermia, acidosis and coagulopathy, and morbidity increases substantially in unselected trauma patients if a temperature below 35°C is documented in the first 24 hours.⁹ Shivering can present logistic problems in the ICU and may even need neuromuscular blockade for control. Finally, rebound cerebral oedema has been described in the rewarming phase,¹⁰ and it is unclear how quickly these patients can be rewarmed. Selective cooling of the brain may minimise the risks of systemic hypothermia while still utilising the effects of hypothermia on the CNS.

One observational study examined severe TBI patients who received hypothermia as part of a protocol for refractory intracranial hypertension.¹¹ Arterial (PaO₂) and brain (PbO₂) oximetry, and arterial and brain temperatures were monitored continuously, using an indwelling femoral artery catheter and a cranial bolt. Brain temperature was consistently 0.4°C above arterial blood temperature. PbO₂ decreased with temperature, with a significant reduction below 35°C. Lower brain temperatures than this may therefore impair brain tissue oxygenation and possibly harm neurological outcomes.

Non neurotrauma indications

The most spectacular benefits of hypothermia have been seen in patients post ventricular fibrillation cardiac arrest. Patients were cooled for either 12 or 24 hours in two phase III studies and significant improvements in neurological outcomes were seen. Hypothermia post VF arrest is now a standard recommendation from the International Liaison Committee on Resuscitation.¹⁴

The second group for whom there is a clear benefit is neonatal hypoxic ischaemic encephalopathy of

intermediate severity, as judged by amplitude integrated EEG (the CoolCap study¹⁵). In *a priori* subgroups there was no benefit in the severest injuries, with loss of background amplitude on the aEEG, but a clear neurological benefit was seen at 18 months in the intermediate severity group, OR 0.42 [95% CI 0.22 - 0.80, p = 0.009].

At the other end of the spectrum, there is clearly no neurological advantage to using hypothermia in elective neurovascular surgery. In the recently completed Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST)¹⁶ there was no difference in mortality or good outcomes, but significantly more bacteraemia was seen in the hypothermia group.

Other postulated indications include acute stroke, for which there have been pilot studies such as COOL AID,¹⁷ and to manage uncontrolled intracranial hypertension in acute liver failure.¹⁸

Early clinical trials in TBI

Since 1992 there have been 15 published randomised controlled trials of therapeutic hypothermia in TBI, and since 2001 there have been four systematic reviews. Most of these trials were small single centre trials, and underpowered to show a difference. Only three studies had recruited more than 100 patients.¹⁹⁻²¹ Most studies have shown that hypothermia decreases intracranial pressure. Two suggested there was only a benefit in less severe head injury (presenting with a GCS from 5 to 7). The systematic reviews varied in their inclusion criteria. Henderson *et al*,²² included eight studies, finding an OR of poor neurological outcome 0.75 [95% CI 0.56 - 1.01, p = 0.06] but OR for pneumonia in the normothermic group 0.42 [95% CI 0.25 - 0.70, p = 0.001]. McIntyre *et al*,²³ included twelve studies and looked specifically at the subgroup of patients who were hypothermic for more than 48 hours, with relative risk of poor outcome RR 0.65 [95% CI 0.48 - 0.89] in this group. Harris *et al*,²⁴ evaluated 7 studies. All of their meta analyses were non significant, though an increase in the incidence of pneumonia, cardiac arrhythmias and coagulopathy was noted. The Cochrane collaboration²⁵ evaluated 14 studies and found a non significant improvement in unfavourable outcomes OR 0.75 [95% CI 0.56 - 1.00] but a significant increase in the incidence of pneumonia OR 1.95 [95% CI 1.18 - 3.23]. The four systematic reviews reached the following conclusions respectively: 'hypothermia is not beneficial in the management of severe head injury', 'the evidence is not yet sufficient to recommend routine use of hypothermia for TBI outside of research settings', 'conclusions regarding the use of hypothermia are controversial and not strongly supported by the available evidence', and 'it would

seem inappropriate to use this intervention outside of controlled trials in subgroups of patients for whom there is good reason to think the treatment would be beneficial'.

National Acute Brain Injury: Hypothermia trial

The National Acute Brain Injury: Hypothermia (NABIS:H) trial²⁰ recruited severe TBI patients between age 16 and 65, with GCS 8 after resuscitation. The trial was designed to recruit 500 patients but was terminated for futility at 392 after an interim analysis. Patients were randomised to either normothermia (36 - 37°C) or hypothermia (33°C) which was initiated within 6 hours of presentation and maintained for 48 hours by surface cooling. Other treatment was standardised. The primary endpoint was six month neurological outcome as assessed by the dichotomised Glasgow Outcome Score. 193 patients received standard treatment and 199 standard treatment with hypothermia. Randomisation occurred after 4.2 ± 1.1 hours, and 33°C was achieved by 8.4 ± 3.0 hours in the hypothermia group. 57% of both groups had a poor outcome (severe disability, vegetative state or death) with 28% vs 27% mortality ($p = 0.79$). No benefit was seen in any of the *a priori* subgroups, which were GCS 3 - 4 vs 5 - 8 on admission, and age > 45 years vs ≤ 45 years. Patients in the hypothermia group had more hospital days with complications. Fewer hypothermia patients had elevated intracranial pressure (defined as > 20 mmHg).

Specifically, more of the hypothermia patients required vasopressors to maintain CPP, and those who received them required support for longer. The hypothermia patients had a higher cumulative fluid balance and higher daily mean TISS score (therapeutic intervention scoring system) suggesting they were more complicated to look after in the ICU. The hypothermia patients had at least one complication on 78% of days, compared with 70% of days in the normothermia group. Of greatest concern 10% of the hypothermia group had critical hypotension (MAP < 70 mmHg for two or more consecutive hours) but only 3% of the normothermia patients did. Bradycardia associated with hypotension was seen in 16% of the hypothermia patients and only 4% of the normothermia group.

The authors conclude "treatment with hypothermia, with the body temperature reaching 33°C within eight hours after injury, is not effective in improving outcomes in patients with severe TBI".

Where did NABIS:H 'go wrong'?

Post hoc analyses have highlighted a number of points in the NABIS:H study.

1. Patients who were hypothermic on admission and then rewarmed did worse than those who remained

hypothermic, with 78% vs 61% poor outcomes ($p = 0.09$).²⁶

2. Patients over 45 years old randomised to hypothermia did poorly, with 88% poor outcomes including 38% mortality (compared with 69% poor outcomes including 38% mortality if randomised to normothermia, $p = 0.08$), and many more complications (82% of days vs 55% of days experiencing complications).
3. Patients over 45 years who were hypothermic on admission did appallingly in either group (93% vs 86% poor outcomes. $P = 0.60$)
4. Patients less than or equal to 45 years who were hypothermic on admission did worse if randomised to normothermia compared to hypothermia, 52% vs 76% poor outcomes ($p = 0.02$)
5. Four centres randomised 80% of patients in the study. There were differences in intercentre outcomes ($p = 0.054$), possibly related to an increased incidence of hypotension and low cerebral perfusion pressure. The authors suggest 'the participation of small centres increased intercentre variance and diminished the quality of data'.²⁷

These data indicating that younger patients presenting already hypothermic did much better if not rewarmed suggest either there is a narrow treatment window, or that rewarming is deleterious to these patients. Animal research is more supportive of the former²⁸ though of course both explanations may be correct.

Where to next?

There are a number of other clinical trials underway at present.

NABISH II

A follow-up trial by the NABIS group²⁹ is looking at the specific subgroup who appeared to benefit from hypothermia in NABIS:H. Patients with suspected head injury aged between 16 and 45 will be cooled to 35°C within 2 hours of injury. If possible cooling will be initiated prehospital using surface cooling, otherwise it will be initiated as soon as possible in the emergency department. If the patient fits inclusion criteria he or she will then be randomised to cooling to 33°C for 48 hours before gradual rewarming, or early rewarming to normothermia. This trial specifically tests the hypothesis that there is a very short treatment window for hypothermia induction.

Paediatric trials

It is suggested that hypothermia is safer in children than in adults. Isolated head injury is relatively more common, rather than the multisystem trauma seen in adults, and nosocomial pneumonia is rarely life

threatening. Two North American trials currently underway are assessing 24 hours hypothermia in children in severe TBI. Of these the Canadian HypHIT trial³⁰ is due to report later in 2005 and the US Hypo1 trial has recently reported phase 2 results.³¹ The Australasian HiTBIC trial (Hypothermia in Traumatic Brain Injury in Children) is currently being planned. It will study prolonged initial hypothermia (minimum 72 hours at 32 - 33°C) compared with normothermia, looking at good outcomes at 12 months, defined as paediatric cerebral performance categories (PCPC) 1-3.

Summary

It is by no means clear in June 2005 that the benefits of hypothermia in traumatic brain injury outweigh the risks. If induced hypothermia is indeed beneficial there are a number of significant questions which need to be answered. These include how soon must cooling be started to be effective, how deep must it be to work, how deep is too deep, for how long must hypothermia be continued, and how quickly should patients be rewarmed. Until these questions are answered and the benefit clearly demonstrated in a randomised controlled trial then induced hypothermia must be considered too risky and should not be used in traumatic brain injury outside the context of a trial.

Received 10 June 05

Accepted 30 June 05

REFERENCES

- Fay T. Observations on prolonged human refrigeration. *NY State Med J* 1940;40:1351-1354, and Fay T, Observations on generalized refrigeration in cases of severe cerebral trauma. *Assoc Res Nerv Ment Dis Proc* 1943;24:611-619.
- Bigelow WG, Callaghan JC, Hopps VA. General hypothermia for experimental intracardiac surgery: use of artificial pacemaker for cardiac standstill and cardiac rewarming in general hypothermia. *Ann Surg* 1950;132:531-543.
- Sedzimir CB. Therapeutic hypothermia in cases of head injury. *J Neurosurg* 1959;16:407-414.
- Clifton GL. Is keeping cool still hot? An update on hypothermia in brain injury. *Curr Opin Crit Care* 2004;10:116-119.
- Busto R, Dietrich WD, Globus MYT, et al. Small differences in intraschaemic brain temperature critically determine the extent of ischaemic neuronal injury. *J Cereb Blood Flow Metab* 1987;7:141-148.
- Kurz A, Sessler D and Lenhardt R. Perioperative normothermia to reduce incidence of surgical-wound infection and shorten hospitalization. *N Engl J Med* 1996;334:1209-1215.
- Polderman KH, Peerdeman SM, Girbes AR. Hypophosphatemia and hypomagnesemia induced by cooling in patients with severe head injury. *J Neurosurg* 2001;94:697-705.
- Rohrer MJ, Natale AM. Effect of hypothermia on the coagulation cascade. *Crit Care Med* 1992;20:1402-1405.
- Gunning KA, Sugrue M, Sloane D, Deane SA. Hypothermia and severe trauma. *Aust NZ J Surg* 1995;65:80-82.
- Iida K, Kurusu K, Arita K, Ohtani M. Hyperemia prior to acute brain swelling during rewarming of patients who have been treated with moderate hypothermia for severe head injuries. *J Neurosurg* 2003;98:793-799.
- Gupta AK, Al-Rawi PG, Hutchinson PJ, Kirkpatrick PJ. Effect of hypothermia on brain tissue oxygenation in patients with severe head injury. *Br J Anaesth* 2002;88:188-192.
- Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *New Engl J Med* 2002;346:557-563.
- The Hypothermia After Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002;346:549-556.
- Nolan JP, Morley PT, Van den Hoek TL, et al. Therapeutic hypothermia after cardiac arrest. An advisory statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation. *Resuscitation* 2003;57:231-235.
- Gluckman PD, Wyatt JS, Azzopardi D, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. *Lancet* 2005;365:663-670.
- Todd MM, Hindman BJ, Clarke WR, Torner JC for the IHAST investigators. Mild intraoperative hypothermia during surgery for intracranial aneurysm. *New Engl J Med* 2005;352:135-145.
- De Georgia MA, Krieger DW, Abou-Chebl A. Cooling for acute ischaemic brain damage (COOL AID). *Neurology* 2004;63:312-317.
- Jalan R, Damink SWMO, Deutz NEP, et al. Moderate hypothermia for uncontrolled intracranial hypertension in acute liver failure. *Lancet* 1999;354:1164-1168.
- Zhang K, Wang J. Comparative study on mild hypothermia in patients with severe head injury and the most severe head injury. *Inner Mongolia Med J* 2000;32:4-6.
- Clifton GL, Miller ER, Choi SC et al. Lack of effect of induction of hypothermia after acute brain injury. *N Engl J Med* 2001;344:556-563.
- Zhi D, Zhang S, Lin X. Study on therapeutic mechanism and clinical effect of mild hypothermia in patients with severe head injury. *Surg Neurol* 2003;59:381-385.
- Henderson WR, Dhingra VK, Chittock DR, et al. Hypothermia in the management of traumatic brain injury. A systematic review and metaanalysis. *Intens Care Med* 2003;29:1637-1644.
- McIntyre LA, Fergusson DA, Hebert PC, et al. Prolonged therapeutic hypothermia after traumatic brain injury in adults: a systematic review. *JAMA* 2003;289:2992-2999.

24. Harris OA, Colford JM, Good MC, Matz PG. The role of hypothermia in the management of severe brain injury: a metaanalysis. *Arch Neurol* 2002;59:1077-1083.
25. Alderson P, Gadkary C, Signorini DF. Therapeutic hypothermia for head injury. *The Cochrane Database of Systematic Reviews* 2004;Issue 4CD001048.pub2.
26. Clifton GL, Miller ER, Choi SC, et al. Hypothermia on admission in patients with severe brain injury. *J Neurotrauma* 2002;19:293-301.
27. Clifton GL, Choi SC, Miller ER, et al. Intercenter variance in clinical trials of head trauma – experience of the National Acute Brain Injury Study: Hypothermia. *J Neurosurg* 2001;95:733-734.
28. Markgraf CG, Clifton GL, MoodyMR. Treatment window for hypothermia in brain injury. *J Neurosurg* 2001;95:979-983.
29. www.clinicaltrials.gov/ct/gui/show/NCT00040339 [accessed April 24th, 2005], and Clifton GL [personal communication]
30. www.cheori.org/Hyp-HIT/hyp_summary.htm [accessed April 24th, 2005].
31. Adelson PD, Ragheb J, Kanev P, et al. Phase II clinical trial of moderate hypothermia after severe traumatic brain injury in children. *Neurosurgery* 2005;56:740-754.