Therapeutic hypothermia, still "too cool to be true?"

F1000Prime REPORTS

Published: 01 July 2013

Therapeutic hypothermia, still "too cool to be true?"

Alistair Gibson[2] and Peter J. D. Andrews[1]*

Addresses: [1]Centre for Clinical Brain Sciences, and [2]Department of Anaesthesia & Critical Care, University of Edinburgh & NHS Lothian, Western General Hospital, Edinburgh, United Kingdom, EH12 6ER

* Corresponding author: Peter J D Andrews (P.Andrews@ed.ac.uk)

F1000Prime Reports 2013, **5**:26 (doi:10.12703/P5-26)

Abstract

Therapeutic hypothermia, an intervention reducing core body temperature below 35 degrees Celsius, has gained popularity in the management of acute brain injury after a series of small clinical trials in patients following cardiac arrest, stroke and traumatic brain injury. This article reviews the evidence relating to therapeutic hypothermia as an intervention in acute injury.

Introduction

Acute brain injury of any aetiology can cause sudden and tragic loss of life or long-term disability. Acute brain injury syndromes include traumatic brain injury, cardiac arrest or stroke and have a considerable social and economic consequence.

Therapeutic hypothermia, an intervention reducing core body temperature below 35 degrees Celsius, has gained popularity in the management of acute brain injury following a series of small clinical trials in patients following cardiac arrest, stroke and traumatic brain injury. It is believed that therapeutic hypothermia provides prophylactic neuroprotection following an ischaemic neuronal insult. However, the evidence is generally weak with neonatal hypoxic ischaemic encephalopathy being the only clinical setting where there is evidence, with a low risk of bias, in support of prophylactic neuroprotection of therapeutic hypothermia.

Therapeutic hypothermia is not a recent concept, first described by Fay [1] in 1945 who described cooling patients after traumatic brain injury. Successful use of therapeutic hypothermia after cardiac arrest in humans was also described in the late 1950s [2,3]. However, the use of therapeutic hypothermia did not become common place until the 1990s, owing to the perception that therapeutic hypothermia caused many side effects including pneumonia, bleeding and cardiac arrhythmias. Renewed interest followed the publication of promising experimental data demonstrating that hypothermia resulted in less neuronal damage and offered cerebral protection against ischaemia [4-6]; thereafter, several small, single-center clinical trials were carried out and showed promising results prompting the initiation of larger multicenter trials.

This article appraises the publicly available evidence relating to therapeutic hypothermia as an intervention in acute brain injury to date.

Theraputic hypothermia in practice

How does it work?

The goal is to improve functional outcomes through neuroprotection of neural tissue following an acute brain injury.

Therapeutic hypothermia is pleiotropic and potential mechanisms by which it is believed to prevent neuronal cell death are outlined below [7].

1. Creating a favourable balance between oxygen supply and demand by reducing cerebral metabolic rate.

2. Preventing or reducing the disruption of the blood-brain-barrier by reducing arteriole permeability and, as a result, reducing the formation of cerebral oedema.

3. Reduced free radical formation.

4. Decreased inflammatory response, including a reduction in the release of pro-inflammatory cytokines and polymorphonuclear leukocyte adhesion in the damaged brain.

5. Reduced seizure activity, which in turn reduces the cerebral metabolic rate and ischaemia potential.

6. Reduced apoptosis, a common finding in all forms of central nervous system (CNS) injury.

7. A reduction in the production of excitatory neurotransmitters, such as glutamate.

Methods of cooling

Cooling is often considered under the headings 'induction' and 'maintenance'. Induction of hypothermia requires careful patient preparation, including increased sedation, focal body warming and detection and management of shivering. Effective methods for induction of therapeutic hypothermia include rapid intravenous infusion of 20-30 ml/kg refrigerated 0.9% sodium chloride (inexpensive) and intravascular cooling catheters or intra-nasal nebulised perflourocarbon (Rhinochill, PhysioControl) both of which incur significant cost.

Maintenance of hypothermia is frequently delivered by surface cooling, with or without closed-loop feedback. Some of these devices use reusable blankets, which are less effective but are inexpensive, or water circulating hydrogel heat exchange pads, which are efficient but have an associated significant cost (approx £500/patient in the UK). Inexpensive surface cooling with icepacks can lead to variable temperature control with potential for undesirable high and low temperatures and can be labor intensive. Core cooling is achieved by the use of intravascular catheters, which achieve rapid cooling with reliable closed-loop maintenance of desired temperature. However, it involves the use of an invasive procedure and has associated procedure- and device-specific risks.

Alternatively, extracorporeal circuits such as cardiopulmonary bypass circuits can be used; these are quick and effective in achieving hypothermia but are impractical in the intensive care unit (ICU) setting and highly invasive. It is common to use a combination of core (induction) and surface cooling (maintenance) techniques to achieve the desired rapid cooling and then to provide maintenance of hypothermia.

A third option of direct brain cooling has been suggested as an alternative but is not yet in widespread clinical use.

Scenario

Cardiac Arrest

In animal models and clinical studies, therapeutic hypothermia after the return of spontaneous circulation showed improvement in functional outcome [8]. Therapeutic hypothermia is now recommended in several national and international guidelines for management of patients who have persistent coma following return of spontaneous circulation after cardiac arrest [9-15]. The main evidence on which these recommendations are based comes from two publications, Bernard et al. [16] and HACA [17] from 2002, who cooled their patients for 12-24 hours to a target temperature of 32-34 degrees Celsius. Both studies only looked at patients who suffered an out-of-hospital cardiac arrest where the initial rhythm was ventricular fibrillation and the aetiology was known to be cardiac in origin; all other aetiologies and arrhythmias were excluded. However, recommendations have been extrapolated to include all cardiac arrests where the coma persists. Both these studies were small, suffered from problems of heterogeneity or were at high risk of bias, yet they are used as the rationale for instituting therapeutic hypothermia. These data have spawned several additional studies seeking to replicate these results in all cardiac arrests with return of spontaneous circulation and persistent coma; however, this has never conclusively been demonstrated and the risks and benefits of therapeutic hypothermia in these settings remain unknown. The HACA and Bernard studies [16,17] would have benefited from increased size, blinding and from improvements in randomization in order to reduce the risk of bias. Post-hoc analysis of the control group of the Bernard paper showed some support for normothermia, associated with improved outcomes – compared with pyrexia – but therapeutic hypothermia (the intervention) provided a significant benefit versus the normothermic patients. Following these studies, a number of other investigators have demonstrated significant improvements from therapeutic hypothermia in before-and-after studies. It is therefore plausible that therapeutic hypothermia is of benefit in patients whose initial rhythm is ventricular fibrillation, but the data do not currently exist to support therapeutic hypothermia in cardiac arrest where ventricular fibrillation is not the initial rhythm.

Traumatic Brain injury

The most important feature of traumatic brain injury resuscitation is that no therapeutic intervention has been demonstrated to improve outcome. Therapeutic hypothermia after traumatic brain injury is often delayed due to resuscitation, stabilisation and investigation of the polytrauma patient who may have more immediate treatment priorities. It is also believed that hypothermia may be contraindicated in the multiply injured patient as it may contribute to coagulopathy.

To date, eight meta-analyses have been conducted to determine the usefulness of therapeutic hypothermia in the management of traumatic brain injury. These meta-analyses have shown that no high-quality randomized controlled trials have been conducted in this area as yet, that all studies differ in their protocols and not all studies include adequate allocation concealment and randomization [7]. A Cochrane review on therapeutic hypothermia in traumatic brain injury from 2009 [18] showed that there may be therapeutic benefit in the use of hypothermia in severe traumatic brain injury, with a reduction in mortality and improved neurological outcomes. However, significant benefit could only be identified from low-quality trials and the higher quality multicenter trials found no statistical difference in the likelihood of death following a traumatic brain injury, whether managed with therapeutic hypothermia or not. All of these studies have examined the use of early (first six hours after injury) prophylactic therapeutic hypothermia, delivered for neuroprotection. In clinical practice, therapeutic hypothermia is commonly used for intracranial pressure reduction, although there are no trials that have tested this hypothesis and reported so. It has been shown that prophylactic hypothermia reduced intracranial pressure in patients with traumatic brain injury and raised intracranial pressure, although in most cases this was not a significant finding [7].

Stroke

Currently, the only proven treatments for ischaemic stroke in the acute setting are thrombolysis and antiplatelet therapy. Therapeutic hypothermia has been suggested as a treatment modality to provide neuroprotection in this setting, but is not considered to be an alternative to thrombolysis, as restoration of oxygen supply to affected areas will always provide better conditions for neuronal recovery. However, after arterial ischemic stroke, therapeutic hypothermia is considered as an adjunct to limit ischaemic injury. Hypothermia has also shown benefit in animal models of cerebral ischaemia, reducing infarct volume by up to 40% [19]. Despite a number of studies into the clinical application of therapeutic hypothermia in acute ischaemic stroke, none have demonstrated outcome benefit.

It is logistically challenging to provide therapeutic hypothermia in the setting of acute ischaemic stroke; the main challenge is that stroke patients are, in the main, awake and do not tolerate cooling, in contrast to cardiac arrest and traumatic brain injury patients who have pharmacologically induced comas. The result is that shivering increases metabolic rate and oxygen demand, and whilst neuromuscular blockade can be used to counteract this in the sedated/anaesthetised patient encountered in the cardiac arrest and traumatic brain injury settings, this is not feasible for stroke patients. This question is the subject of the ongoing Eurohyp1 study (http://www.eurohyp1.eu/).

Duration of hypothermia

It is generally considered to be beneficial to induce hypothermia in as short a period of time after initial injury as possible to provide prophylactic neuroprotection. In the cardiac arrest setting, guidelines vary between 12 and 24 hours for duration of hypothermia before rewarming. Neonatal hypoxic encephalopathy cases are treated for 72 hours, and recent animal data indicates that longer duration might be beneficial in cardiac arrest also.

In traumatic brain injury there is a mounting body of evidence and opinion in favour of continuing hypothermia for a minimum period of 48 hours [20,21]. As long as the intracranial pressure remains high, rewarming seems inappropriate and longer duration of hypothermia might be beneficial, but more data regarding these issues, both for cardiac arrest and traumatic brain injury, are required to give definitive advice.

Side effects

Therapeutic hypothermia is not a risk-free undertaking and has been associated with a number of potential adverse effects that have the potential to offset the potential benefits. However, studies comparing therapeutic hypothermia with normothermia have not found any significant difference in the incidence of severe side effects. In order to identify and treat these complications, patients should be cared for in specialist critical care units. The key complications are described below.

Shivering

This is associated with an increase in sympathetic nervous system activity and an increase in metabolic oxygen demand, which is deleterious during the acute phase of the patient's illness but has been described as a potential predictor of a good outcome in cardiac arrest patients and it may indeed be a biomarker for less severe cerebral injury.

Pneumonia

The Cochrane review of 2009 [18] (traumatic brain injury) showed that, while there was a trend towards an increased risk of pneumonia, this was not significant.

Cardiovascular instability

Hypothermia is associated with both hypotension and arrhythmias (mostly bradycardia). In cardiac arrested patients, this beta blocker-like effect is possibly of benefit [22].

Glucose control

Hyperglycemia is common and it has been shown that persistent hyperglycemia is associated with an increase in mortality [22].

Electrolytes derangement

The most common electrolyte abnormality encountered is hypokalemia; however, routine measurement of plasma potassium, sodium and magnesium should be undertaken.

Rebound intracranial hypertension on rewarming

This is a rise in intracranial pressure during re-warming – a phenomenon described in many previous studies [23].

Summary

In our opinion, the case for therapeutic hypothermia remains "unproven" with the notable exception of neonatal hypoxic encephalopathy. There is sufficient evidence to suggest that it may be of benefit in out-of-hospital ventricular fibrillation cardiac arrest and this has led to its inclusion in a number of national and international guidelines. However, there remains doubt as to the efficacy of therapeutic hypothermia in cardiac arrest where the initial rhythm is not ventricular fibrillation. Currently, there is insufficient evidence from the publicly available trials data to suggest a benefit from therapeutic hypothermia in the provision of neuroprotection or the management of raised intracranial pressure following traumatic brain injury.

Three hypotheses need to be prospectively tested. The first is that therapeutic hypothermia confers prophylactic neuroprotection following traumatic brain injury. The second is that titrated hypothermia reduces intracranial pressure following traumatic brain injury. The third is that therapeutic hypothermia is more effective than normothermia after cardiac arrest. The first of these is being tested by the prophylactic hypothermia trial to lessen traumatic brain injury randomized control trial (POLAR RCT), the second by the Eurotherm3235trial and the third in the Target Temperature Management after out-of-hospital cardiac arrest (TTM study). Hopefully, the results of these trials will provide evidence-based guidelines for clinicians managing these clinical scenarios.

Abbreviations

CNS, central nervous system; ICU, intensive care unit.

Disclosures

The authors declare that they have no disclosures.

References

1. Fay T: **Observations on generalized refrigeration in cases of severe cerebral trauma.** *Assoc Res Nerv Ment Dis Proc* 1945, **24:**611-9.
2. Benson DW, Williams GR, Spencer FC, Yates AJ: **The use of hypothermia after cardiac arrest.** *Anesth Analg* 1959, **38:**423-8.
3. Williams GR, Spencer FC: **The clinical use of hypothermia following cardiac arrest.** *Ann Surg* 1958, **148:**462-8.
4. Ginsberg MD, Busto R: **Combating hyperthermia in acute stroke: a significant clinical concern.** *Stroke* 1998, **29:**529-34.
5. Dietrich WD, Busto R, Halley M, Valdes I: **The importance of brain temperature in alterations of the blood-brain barrier following cerebral ischemia.** *J Neuropathol Exp Neurol* 1990, **49:**486-97.
6. Ishikawa M, Sekizuka E, Sato S, Yamaguchi N, Inamasu J, Bertalanffy H, Kawase T, Iadecola C: **Effects of moderate hypothermia on leukocyte- endothelium interaction in the rat pial microvasculature after transient middle cerebral artery occlusion.** *Stroke* 1999, **30:**1679-86.
7. Sinclair HL, Andrews PJ: **Bench-to-bedside review: Hypothermia in traumatic brain injury.** *Crit Care* 2010, **14:**204.
8. Sterz F, Safar P, Tisherman S, Radovsky A, Kuboyama K, Oku K: **Mild hypothermic cardiopulmonary resuscitation improves outcome after prolonged cardiac arrest in dogs.** *Crit Care Med* 1991, **19:**379-89.

   F1000Prime RECOMMENDED
9. National Institute for Health and Clinical Excellence: **Therapeutic hypothermia following cardiac arrest IPG386.** March 2011.
10. Nolan JP, Morley PT, Hoek TLV, Hickey RW: **Therapeutic hypothermia after cardiac arrest. An advisory statement by the Advancement Life support Task Force of the International Liaison committee on Resuscitation.** *Resuscitation* 2003, **57:**231-5.
11. Resuscitation Council (UK) 2005, **Adult Advanced Life Support.** Resuscitation guidelines 2005 Resuscitation Council (UK).
12. Peberdy MA, Callaway CW, Neumar RW, Geocadin RG, Zimmerman JL, Donnino M, Gabrielli A, Silvers SM, Zaritsky AL, Merchant R, Vanden Hoek TL, Kronick SL: **Part 9: post-cardiac arrest care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care.** *Circulation* 2010, **122:**S768-86.
13. Castrén M, Silfvast T, Rubertsson S, Niskanen M, Valsson F, Wanscher M, Sunde K: **Scandinavian clinical practice guidelines for therapeutic hypothermia and post-resuscitation care after cardiac arrest.** *Acta Anaesthesiol Scand* 2009, **53:** 280-8.
14. **Adult advanced life support: Australian Resuscitation Council Guidelines 2006.** *Emerg Med Australas* 2006, **18:**337-56.
15. **Guidelines for the use of hypothermia after cardiac arrest.** *CJEM* 2006, **8:**106-8.
16. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, Smith K: **Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia.** *N Engl J Med* 2002, **346:**557-63.

   F1000Prime RECOMMENDED
17. The Hypothermia after Cardiac Arrest Study Group: **Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest.** *N Engl J Med* 2002, **346:**549-56.

   F1000Prime RECOMMENDED
18. Sydenham E, Roberts I, Alderson P: **Hypothermia for traumatic head injury.** *Cochrane Database Syst Rev* 2009, CD001048.

   F1000Prime RECOMMENDED
19. van der Worp HB, Sena ES, Donnan GA, Howells DW, Macleod MR: **Hypothermia in animal models of acute ischaemic stroke: a systematic review and meta-analysis.** *Brain* 2007, **130:** 3063-74.

   F1000Prime RECOMMENDED

20. Peterson K, Carson S, Cairney N: **Hypothermia treatment for traumatic brain injury: a systematic review and meta-analysis.** *J Neurotrauma* 2008, **25:**62-71.

F1000Prime RECOMMENDED

21. Stocchetti N, Colombo A, Ortolano F, Videtta W, Marchesi R, Longhi L, Zanier ER: **Time course of intracranial hypertension after traumatic brain injury.** *J Neurotrauma* 2007, **24:**1339-46.

F1000Prime RECOMMENDED

22. Nielsen N, Sunde K, Hovdenes J, Riker RR, Rubertsson S, Stammet P, Nilsson F, Friberg H: **Adverse events and their relation to mortality in out-of-hospital cardiac arrest patients treated with therapeutic hypothermia.** *Crit Care Med* 2011, **39:**57-6.

F1000Prime RECOMMENDED

23. McIntyre LA, Fergusson DA, Hebert PC, Moher D, Hutchison JS: **Prolonged therapeutic hypothermia after traumatic brain injury in adults: a systematic review.** *JAMA* 2003, **289:** 2992-9.