Special Article

Targeted temperature management in brain protection: An evidence-based review

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ABSTRACT

Targeted temperature management (TTM) for neuroprotection involves maintaining the temperature of the brain at predetermined levels by various techniques. It is aimed at avoiding the harmful effects of hyperthermia on the brain and at exploiting the protective effects of lower tissue temperature. There has been an explosion in the use of TTM for neuroprotection in a variety of clinical scenarios apart from the commonly accepted fields of resuscitation and ischaemic, hypoxic encephalopathy. This review briefly discusses the evidence base for TTM. The focus is on various areas of application for neuroprotection, the practical issues pertaining to TTM implementation, the recent data that support it and the present areas of controversy.

Key words: Endovascular cooling, hypothermia, neuroprotection, targeted temperature management, therapeutic temperature management

INTRODUCTION

In the year 1938, Fay was among the first to report 'extremely gratifying results' of cooling the brain by irrigating it directly with ice water.[1] Targeted temperature management (TTM) traditionally refers to deliberate reduction of the core body temperature to a range of 32–34°C (89.6–93.2°F) in patients who don't regain consciousness after return of spontaneous circulation (ROSC) following a cardiac arrest. Decreasing the temperature of the target tissue may involve therapeutic hypothermia (TH) in normothermic patients (mild hypothermia of 33–35°C) or induced normothermia (cooling patients to 37°C) in hyperthermic patients. The term TTM now encompasses both these situations.[2] TTM has been used in many settings, such as for neuroprotection, in cardiac surgeries and hyperthermic emergencies like heat strokes, etc. The purpose of this review is to provide a concise update on the modalities, complications and the areas of clinical application of TTM for brain protection and to make the reader aware of the evidence base for the same. The following databases were accessed: Embase, Medline, CINAHL, Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews; key words used to search the databases were 'therapeutic hypothermia'', 'induced hypothermia', 'cooling post-cardiac arrest' and 'targeted temperature management'.

MECHANISM OF ACTION OF HYPOTHERMIA IN NEUROPROTECTION

Cooling has been shown to reduce primary injury and prevent secondary injury in animal models of brain insult and certain clinical settings.[3] Hypothermia affects pathways leading to excitotoxicity, apoptosis, inflammation and free radical production, as well as blood flow, metabolism and blood-brain barrier integrity. Hypothermia may also influence neurogenesis, gliogenesis and angiogenesis following the injury [Figure 1]. It is likely that no single factor can explain the neuroprotection provided by hypothermia, but understanding its myriad effects may shed light on its neuroprotective mechanisms.[4]

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ESTABLISHMENT OF HYPOTHERMIA

The establishment of hypothermia therapy (HT) can be divided into three phases: induction, maintenance and re-warming [Figure 2]. The goal of the induction phase is to achieve the target body temperature as quickly as possible for which modalities may vary [Table 1]. The target temperature is controlled at the set levels during the maintenance phase of TTM for duration of 24–48 h depending on institute protocols. At the end of the maintenance phase, the patient's temperature is allowed to rise gradually at a rate of 0.15–0.5°C per hour. The

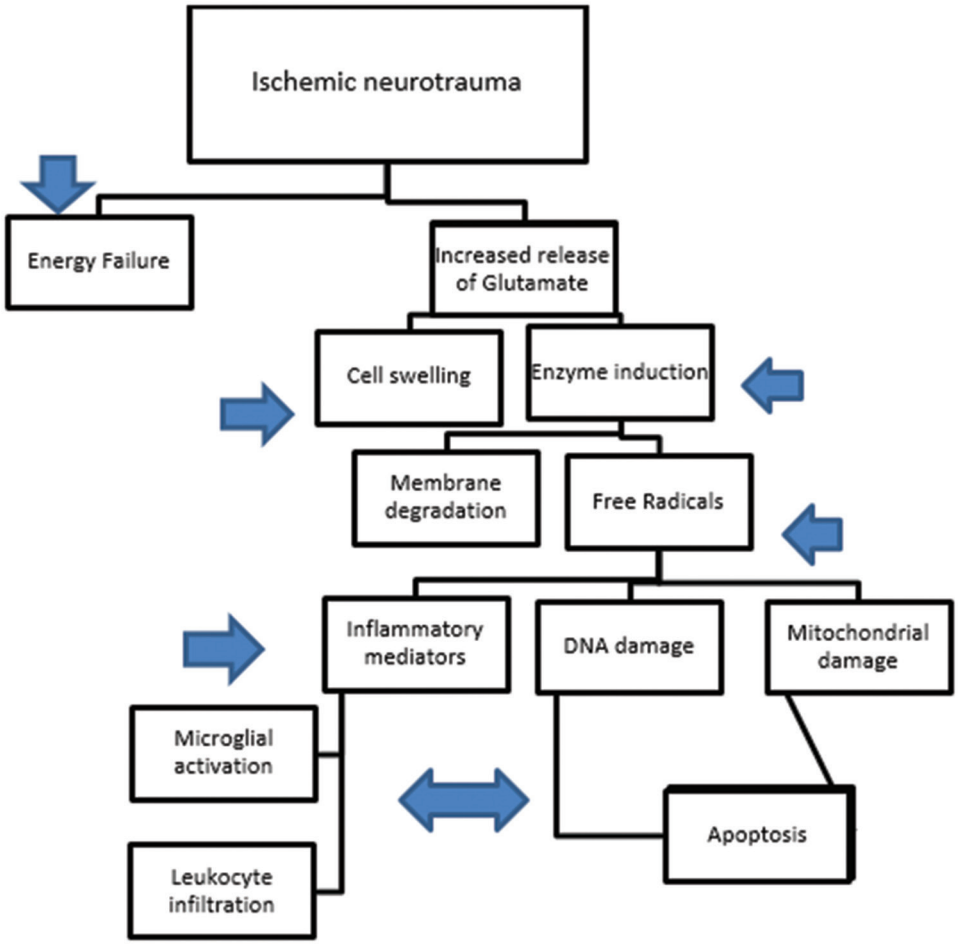

Figure 1: Neuroprotective mechanism of hypothermia – bold arrows depict the multiple stages at which hypothermia decreases the effects of the primary insult

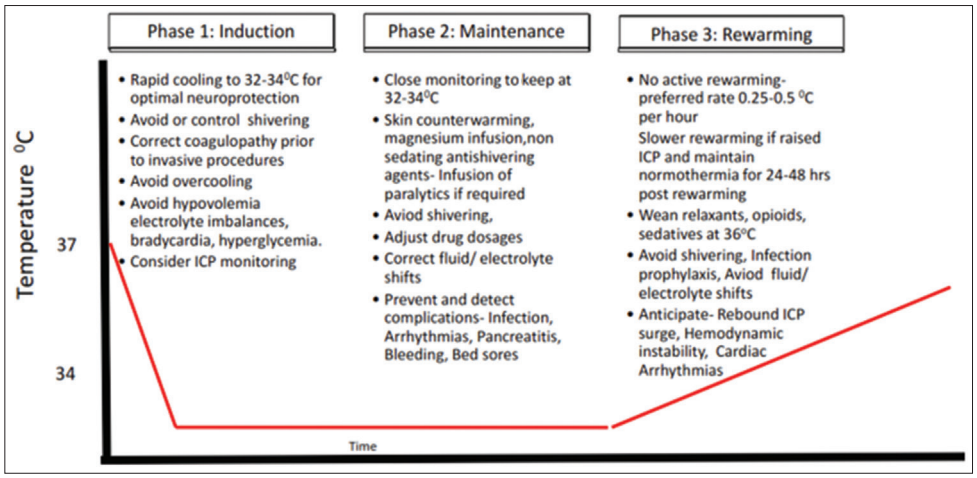

Figure 2: Three phases of targeted temperature management

optimal time point to start or terminate hypothermia in different clinical situations is still not known. The current European resuscitation guidelines recommend starting hypothermia as soon as possible after ROSC.

Table 2 lists the complications known to be associated with cooling during TTM

Shivering

In healthy humans, peripheral vasoconstriction is triggered at 36.5°C and shivering starts at 35.5°C. Temperature thresholds for vasoconstriction and shivering are often higher than normal in brain-injured patients. Control of the shivering is essential for effective cooling, as shivering increases oxygen consumption and fights the cooling process making attaining target temperature difficult. It is extremely uncomfortable. Pharmacological strategies to counteract such a response are to use benzodiazepines for sedation, an opioid analgesic and systemic neuromuscular blockade for muscle relaxation. The combination of meperidine (± buspirone), skin warming and magnesium infusion can be used to reduce shivering and avoid thermal discomfort.[3]

Cardiovascular manifestations

Induced hypothermia may result in bradycardia, vasoconstriction and a slight increase in arterial pressure after the induction phase due to increased systemic vascular resistance. Post-cardiac arrest victims may develop hypotension as a part of the post-cardiac arrest syndrome of myocardial dysfunction, ischaemia reperfusion or cold diuresis. Although TTM has not been associated with the development of arrhythmias in randomised controlled trials or in observational studies, persistent arrhythmias can develop as a consequence of over-cooling (≤32°), electrolyte imbalance, or tubular dysfunction.[3,11]

Table 1: Cooling techniques

Conventional cooling methods: The infusion of cold fluid has been shown to be effective for the induction phase. Infusion of 500-2000 ml of normal saline (4°C) intravenously has been shown in a randomised trial to be effective in lowering the arrival hospital temperature without adverse consequences in terms of blood pressure, heart rate, arterial oxygenation, risk of pulmonary oedema or re-arrest.[5] The efficacy for cold infusion alone versus that with the use of ice bags or other cooling devices for tight maintenance of the target temperature is debated.[6] Although cost effective and easily available, this technique requires a high degree of commitment of the personnel while the control may not be very precise

External cooling techniques: A number of commercially available cooling devices, including cooling mattresses, air-filled or water circulating cooling blankets and garment-type surface cooling devices are available which allow more precise temperature regulation than ice bags or cold saline infusion. However, they are expensive and have been associated with adverse skin reactions like skin erythema and mottling[7]

Endovascular cooling techniques: Consist of an endovascular cooling catheter inserted percutaneously into a central vein and connected to an automatically guided temperature cooling system. This system extracts heat directly from the core, is not impaired by thermoregulatory cutaneous vasoconstriction allowing rapid and accurate establishment of the target temperature and gradual rewarming. Requirement for central venous cannulation, venous thrombosis, infection, and costs are presently the main concerns in the routine use of these devices[8]

Novel cooling techniques: These include iced saline gastric lavage, cooling helmets, a total cold water immersion system, automated peritoneal lavage and trans-nasal cooling devices that allow rapid induction of hypothermia to a core temperature of 34°C[9,10]

Table 2: Complications of cooling

System	Effect
Cardiovascular	Hypertension, tachycardia, venous thrombosis, myocardial infarction
Coagulation	Coagulopathy, activated platelets
Dyselectrolytemia	Hypokalaemia, hypomagnesemia, hypophosphatemia
Immune	Surgical site infections, nosocomial infections
Endocrine	Steroids and insulin, thyroid stimulating hormone
Musculoskeletal	Shivering
Drug metabolism	Delayed clearance

Infection

Data from clinical studies do not provide uniform answers whether the chance of increase in the rate of infections as a consequence of hypothermia-induced impairment of cellular and humoral immunity is of clinical significance. The risk appears to increase with prolonged use, and careful monitoring is required in these patients. Prophylactic antibiotics may be considered in high-risk patients, who receive hypothermia for a prolonged period.[12]

Bleeding

Hypothermia might result in an increased risk of bleeding as a result of impaired platelet function, thrombopenia and impairment of the coagulation cascade. Such risks have not been observed, however, in clinical practice when hypothermia has been used in isolation or in combination with percutaneous coronary intervention techniques.[7] Although the risks may increase significantly in moderate-to-severe acidosis, no effects of hypothermia on coagulation have occurred in any patient as long as the temperature is ≥35°C, and patients at very high bleeding risk can safely be cooled to this temperature.[13]

Alterations in drug metabolism

Hypothermia leads to slowing of a number of hepatic enzymes including the cytochrome P450. Therefore,

drugs that are metabolised by the liver such as sedative and neuromuscular blocking agents will require dose modification.[3]

REWARMING

Rewarming or cessation of active cooling techniques is the third phase of any form of TTM. Temperature control is important during rewarming. Warming the patient too quickly or allowing continued shivering may result in various complications [Table 3]. Controlled rewarming of 0.15°–0.5°C/h is recommended. Adverse consequences of rewarming on the whole body may seriously limit the protective effects of hypothermia, leading to secondary injury such as raised intracranial pressure and cognitive dysfunction among others.[14] Understanding, predicting, and managing possible systemic side-effects of rewarming is important for guaranteeing the efficacy of TTM.

CLINICAL AREAS OF APPLICATION OF TARGETED TEMPERATURE MANAGEMENT

Prehospital cardiopulmonary resuscitation and post-resuscitation

Mild hypothermia is widely used in the treatment of successfully resuscitated patients after cardiac arrest [Table 4]. Two clinical landmark studies in 2002 demonstrated that the use of TH after cardiac arrest due to ventricular fibrillation decreases mortality and improves neurological outcome. Hypothermia can be efficiently induced in the prehospital environment, and the use of mild TH is gaining acceptance. The use of TH after cardiac arrest as soon as possible after ROSC is now recommended.[15-18] A recent trial concludes that in unconscious survivors of out-of-hospital cardiac arrest of presumed cardiac cause, hypothermia at a targeted temperature of 33°C did not confer a benefit as compared with a targeted temperature of 36°C.[19]

Cooling in neurosurgery, neurology, and the intensive care unit

Traumatic brain injury

Clinical trials of hypothermia and temperature management for severe traumatic brain injury (TBI) are divided into trials in which hypothermia is used to treat elevated intracranial pressure[20] and those in which hypothermia is intended as a neuroprotectant, irrespective of intracranial pressure. The brain trauma foundation guidelines summarise that prophylactic hypothermia may improve outcomes if maintained for 48 h or more; but lack in clear mortality benefits (level III evidence). Having enrolled 232 patients and observing no benefits of early induction of hypothermia, the national acute brain injury study hypothermia II (NABISH-II) trial was terminated for futility.[21] A subsequent subgroup analysis of patients in the NABISH I and II trials demonstrated that induction of hypothermia to 35°C before or soon after craniotomy with maintenance at 33°C for 48 h thereafter may improve outcome of patients with haematomas and severe TBI.[22]

Spinal cord injury

In animal models with spinal cord injury, improvements in functional outcome associated with cooling have been reported, and hypothermia has been shown to increase the duration of ischemia required to produce neurological deficits.[23] Thermoregulatory disturbances and fever due to other causes are common in these patients and if not controlled promptly may lead to worsening morbidity and mortality in this group. Hypothermia appears to be a promising treatment in this population as observed in small-scale human studies and needs to be studied in larger prospective clinical trials.[24,25]

Acute ischaemic stroke

Although many arguments favour the successful

Table 3: Complications of rewarming

Core temperature after drop
Vasodilation related hypotension
Acid base imbalance, changes in electrolytes-hyperkalaemia and hypophosphatemia
Rhabdomyolysis
Ventricular fibrillation
Paralytic ileus, bladder atony
Hyperglycaemia
Bleeding diathesis

Table 4: Inclusion and exclusion criteria for TTM after cardiac arrest

Inclusion criteria
Cardiac arrest with ROSC
Persistent coma after ROSC
Adequate blood pressure can be maintained either spontaneously or with fluids/pressors
Known time of cardiac arrest (downtime <1h)
Exclusion criteria
Coma due to identifiable reason other than the cardiac arrest
Responsive to verbal stimuli after cardiac arrest
Pregnancy
Terminal illness
Coagulopathy or active bleeding (will consider patients who were anticoagulated before arrest)

TTM – Targeted temperature management; ROSC – Return of spontaneous circulation

translation of TH to stroke patients, available data from clinical studies are not sufficient to recommend TTM for the routine treatment of acute ischemic stroke. The EuroHYP-1 study-an ongoing trial, with 1500 target patients will investigate whether hypothermia administered for 24 h, will improve the neurological outcome in ischemic stroke patients treated within 6 h from symptom onset; the ICTuS trial similarly aims at employing endovascular hypothermia induced within 6 h of stroke onset.[26,27]

Intracranial haemorrhage

Notwithstanding the concerns of hypothermia on platelet function and coagulation profile, experimental data indicate that TTM is neuroprotective after intra cerebral haemorrhage (ICH) and reduces perihaemorrhagic oedema.[28] There is no large-scale data to recommend the use of hypothermia in this group. The results of the on-going cooling in ICH (CINCH) trial are awaited. The CINCH trial will evaluate 50 patients with large primary ICH of the basal ganglia or thalamus within 6–18 h after symptom onset randomly allocated to TH or conventional temperature management.[29]

Cooling in the operation theatre and for subarachnoid haemorrhage

Deep intra-ischaemic hypothermia can be used in cardiothoracic and neurosurgery for the management of congenital heart disease, thoracic aneurysms, and intracranial aneurysms. Although hypothermia is often used during brain surgery, clinical efficacy has not yet been established. In a recent Cochrane review of cooling for cerebral protection during brain surgery, involving 1219 patients the authors found no evidence that hypothermia was either effective or unsafe when compared to normothermia.[30]

So far, the evidence of HT on improved outcome after subarachnoid haemorrhage (SAH) is limited. Intraoperative cooling has been abandoned in all but most carefully selected patients, based on the randomised intraoperative hypothermia study on aneurysm surgery in good-grade SAH patients. The Intraoperative Hypothermia for Aneurysm Surgery Trial applied HT in a randomised study in 1001 patients with good-grade SAH (World Federation of Neurological Surgeons 1–3); however, it found no improvement in neurological outcome 3 months after surgery. Furthermore, there was no evidence for the benefit of intraoperative HT on 24 h and 3 months outcome in patients who underwent temporary clipping.[31]

Therapeutic and prophylactic normothermia

Fever is a very frequent complication of intensive care treatment and an independent predictor of unfavourable outcome and mortality in most patients with an acute severe neurologic injury.[32] Aggressive treatment of fever in the intensive care unit without the side effects of TH led to the concept of controlled prophylactic normothermia-fever reduction with strict maintenance of the body temperature at 36.5°C. Prophylactic and the therapeutic normothermia has been attempted in various clinical scenarios leading to hyperpyrexia as in heat stroke, spinal cord injury, infections of the central nervous system and in refractory status epilepticus.[33-35] The results of the recent apparently 'negative' trial on hypothermia after cardiac arrest have also been discussed on the lines of possibility of active maintenance of temperature of control group at 36°C as being a form of prophylactic normothermia.[19]

Neuroprotection in paediatric and neonatal group

Therapeutic hypothermia has proved to be beneficial in term neonates after hypoxic-ischemic encephalopathy (HIE) and in children with (TBI). Recent reports have also investigated TH for the treatment of super refractory status epilepticus. TH may also represent a useful tool when conventional therapy fails to achieve an effective control of elevated intracranial pressure.[36]

CONCLUSION

There is now a large body of evidence to suggest that temperature regulation and induced hypothermia can be used to limit or prevent injury to the brain in a properly selected category of patients. Clearly, the variables of timing of the initiation of cooling, cooling technique, rate, depth, length of cooling and rewarming all have some effect on mortality and morbidity. However, at this time, these variables are not well studied and are the focus of several current experimental and clinical trials. Evidence in the form of large randomised control trials is needed to enable formal protocols and recommendations in areas other than post-cardiac arrest resuscitation and neonatal HIE.

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