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Review

Therapeutic hypothermia: Benefits, mechanisms and potential clinical applications in neurological, cardiac and kidney injury

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ABSTRACT

Therapeutic hypothermia involves the controlled reduction of core temperature to attenuate the secondary organ damage which occurs following a primary injury. Clinicians have been increasingly using therapeutic hypothermia to prevent or ameliorate various types of neurological injury and more recently for some forms of cardiac injury. In addition, some recent evidence suggests that therapeutic hypothermia may also provide benefit following acute kidney injury.

In this review we will examine the potential mechanisms of action and current clinical evidence surrounding the use of therapeutic hypothermia. We will discuss the ideal methodological attributes of future studies using hypothermia to optimise outcomes following organ injury, in particular neurological injury. We will assess the importance of target hypothermic temperature, time to achieve target temperature, duration of cooling, and re-warming rate on outcomes following neurological injury to gain insights into important factors which may also influence the success of hypothermia in other organ injuries, such as the heart and the kidney. Finally, we will examine the potential of therapeutic hypothermia as a future kidney protective therapy.

Contents

Introduction . . . 843
Cooling: physiological aspects of induction, maintenance and re-warming . . . 844
Potential mechanisms of the neuroprotective effects of therapeutic hypothermia and common side effects . . . 844
What is the clinical evidence? . . . 848
Neurological injury . . . 848
Cardiac injury . . . 850
Kidney injury . . . 850
Hypothermia and AKI . . . 850
Prophylactic hypothermia: POLAR and POLAR-acute kidney injury . . . 851
Acknowledgements . . . 851
References . . . 851

Introduction

Therapeutic hypothermia (TH) involves the controlled reduction of a patient's core temperature in an attempt to protect an organ at risk of injury. To date, TH has principally been used as a protective therapy following various brain insults; however there

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is emerging evidence that it may also be useful in the protection of other organs when at risk of injury.

The current main clinical indications for TH for cerebral protection in adults are out-of-hospital cardiac arrest[1,2] and, in neonates, hypoxic ischaemic encephalopathy[3] with randomised clinical trials showing the neurological benefit of TH.[1] Furthermore, recent meta-analyses have suggested potential outcome benefit with TH following traumatic brain injury (TBI).[4,5] The safety and efficacy of TH have resulted in TH being increasingly applied by clinicians to comatose patients of various etiologies (i.e. stroke, hepatic encephalopathy, etc.) in an attempt to decrease brain injury.[6,7] These new but as yet unproven indications follow from the established use of TH to improve outcomes in operations involving significant risk of cerebral ischaemia during circulatory arrest in cardiac and neurosurgery.[8–10] In addition to its protective neurological effects, hypothermia may decrease infarct size in patients with acute myocardial infarction after emergency percutaneous coronary intervention[11] and reduce the risk of renal failure after renal ischaemia–reperfusion injury in animals.[12,13]

Although evidence is limited, studies suggest five key factors that could explain the failure of these previous studies and need to be addressed in future studies of TH: time to induction of hypothermia after injury, target temperature attained, duration of cooling, rate of re-warming and prevention of side effects/complications from hypothermia. In this article we will review the evidence for potential clinical applications of TH, describe its mechanisms of action and side effects, and, within this setting, discuss optimal methods for its implementation in future clinical trials. The focus is on TBI and on how the lessons learned with TBI may help effectively apply TH to the treatment of acute kidney injury.

Cooling: physiological aspects of induction, maintenance and re-warming

In order to successfully and safely implement cooling, awareness of the physiological effects and appropriate management of the side effects of hypothermia are required. There are 3 commonly recognised phases of hypothermic management: induction, maintenance and re-warming.

In the induction phase the aim is to reduce the temperature to target as quickly as possible. In TBI, clinical studies indicate that the temperature range associated with better outcomes appears to be 32–35 °C[4] (Table 1). As this phase involves the highest risk for immediate side effects such as electrolyte disorders, hyperglycaemia and shivering (Table 1), it is preferable to reach the stable maintenance phase quickly.[14] Continual monitoring of ventilation, blood pressure, sedation, blood sugar, and electrolytes is required in this phase.

Several methods are used to induce hypothermia[14]:

Surface cooling by air: Traditional methods such as exposing the skin to air, which may be combined with sponge baths, are effective, and air-circulating cooling blankets are also available.
Surface cooling by fluid: This includes methods from ice packs to water-circulating cooling blankets, pads, and wrapping garments, as well as hydrogel-coated water-circulating pads.
Core-cooling: The infusion of ice-cold fluids is effective in inducing hypothermia. Invasive devices such as intravascular catheters with saline-filled cold balloons or cooled metal components are also used for core-cooling as well as antipyretic agents.

By combining different cooling methods the target temperature is more rapidly achieved.[14]

In the maintenance phase, core temperature should be tightly controlled to ensure patient stability. During this period, prevention of side effects such as nosocomial infections and pressure ulcers is important particularly if the duration of hypothermia is prolonged.

The re-warming phase involves the very slow increase of the temperature of the patient to normal levels. This is done slowly for several reasons: to minimise electrolyte disturbances caused by shifts between intra- and extracellular compartments, and to reduce insulin sensitivity and the risk for hypoglycaemia if the patient is receiving insulin.[15] Very slow rewarming is also necessary to prevent the exacerbation of damaging mechanisms in the injured brain which are associated with rapid re-warming; and to minimise the degree of vasodilation with warming in an attempt to maintain systemic blood pressure and cerebral perfusion pressure. Following rewarming, hyperthermia is commonly seen. However, normothermia should be maintained since fever is independently associated with adverse outcomes in many forms of brain injury.[14]

Potential mechanisms of the neuroprotective effects of therapeutic hypothermia and common side effects

In out-of-hospital cardiac arrest, hypoxic ischaemic encephalopathy in neonates, traumatic brain injury (TBI), stroke and hepatic encephalopathy, TH is used to reduce the potential neurological complications of evolving secondary brain tissue injury. The mechanisms of action of hypothermia are complex (Table 1) but principally they act to attenuate the cascade of destructive processes (secondary injury), which occurs in the minutes to hours following initial tissue injury (primary injury). We will discuss these processes with particular regard to cerebral insults, where the majority of the research to date has focused, however, these protective processes are expected to be replicated in other organs during TH. Side effects which consequently affect patient management are also addressed (Table 1).

Metabolism/electrolytes: Until the 1990s, it was assumed that the neurological protective effects of hypothermia were solely due to a reduction in cerebral metabolism.[16] Whilst there is indeed a decrease in metabolism, it is now understood that this is only one of many mechanisms behind the protective effects of hypothermia. As the core temperature drops and the metabolic rate decreases, oxygen and glucose consumption, and carbon dioxide production also decrease, thus helping to prevent or ameliorate injury when oxygen supply is interrupted or limited.[17]

The reduction in metabolic rate induced by hypothermia may require adjustments in ventilator settings to maintain normocapnia. Decreases in insulin sensitivity and secretion may also require changes to insulin infusion rates. The rate of these changes depends on the rapidity of induction and rewarming.[14]

Electrolyte levels are also affected by hypothermia due to tubular dysfunction and intracellular shift.[18] Considering that magnesium may ameliorate cerebral injury; that low phosphate levels are linked to higher risk of infection[19]; and that low magnesium and potassium levels can increase the risk of arrhythmias,[19,20] these electrolytes should be kept in the high-normal range during and after hypothermia.[19] However, caution is required with potassium supplementation during cooling as there is a risk of rebound hyperkalaemia during rewarming.

Apoptosis and mitochondrial dysfunction: Following ischaemia with subsequent reperfusion, cells may recover to varying degrees, become necrotic, or enter a pathway to programmed cell death (apoptosis). Whilst hypothermia appears to block the apoptotic pathway in its early stages[21–23] there is a finite window for interventions such as hypothermia to affect this process.

Ion pumps and neuroexcitotoxicity: Hypothermia is thought to inhibit damaging neuroexcitatory processes that occur with ischaemia–reperfusion injury (Fig. 1 and Table 1). When cerebral oxygen supply is interrupted, levels of adenosine triphosphate