Clinical applications of induced hypothermia

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Hypothermia is a well known cause of death, particularly in colder climates; however, it may also be used to preserve life. Defined as a core temperature <35°C, hypothermia as a treatment for medical conditions is not a new practice. Ancient Greek physicians used hypothermia for various conditions including haemorrhage and trauma. More recent use has centred on its efficacy as a neuroprotective strategy. Therapeutic hypothermia was first reported scientifically by Fay in 1940 for the treatment of head injury. Most of the early use of hypothermia was at mild to moderately low temperatures, mainly for cardiac and intracranial aneurysm surgery. The first use of profound hypothermia (<30°C) for head injury was described in 1964; however, its use was restricted because of systemic complications.

Accidental hypothermia causes many deaths in colder parts of the world; a third of persons do not survive temperatures of <28°C. The lowest authenticated body temperature occurred in a Norwegian skier in 1999, who was trapped under ice in a frozen gully. She was successfully resuscitated from being clinically dead but with a core temperature of 13.7°C. Her neurological recovery was complete and she has returned to her work as a doctor!1

The resurgence of interest in mild hypothermia (32–35°C) for neuroprotection in the 1980s resulted form perceived benefit with a lower incidence of severe side-effects. Induced hypothermia in a modern ITU setting can now be achieved in a controlled fashion without the deleterious effects of unintentional overcooling. In certain critical care patient groups, it has demonstrable effects on improving patient outcome.

Mechanisms of action

The effect of hypothermia on the injured brain is complex and not fully understood. It has been established that induced hypothermia has the following mechanisms of action that lead to its neuroprotective effect:

(i) Reduction in cerebral metabolism (CMRO₂) by approximately 7% per 1°C. This leads to less oxygen and glucose consumption.
(ii) Promotion of cerebral vasoconstriction, which can directly decrease ICP. Also vascular permeability and therefore oedema formation is decreased.
(iii) Prevention of neuronal injury leading to programmed cell death (apoptosis) mainly by inhibition of caspase activation.
(iv) Suppression of the inflammatory cascade and decrease nitric oxide, cytokine and leukotriene production. Leukocyte migration from the damaged endothelium is diminished.
(v) Improved ionic homeostasis and blockage of the destructive neuroexotoxic cascade consequent to glutamate accumulation and receptor activation, and subsequent intracellular calcium overload.
(vi) Decreased free radical formation.
(vii) It allows for the cerebral regional temperature differences of 2–3°C that are known to exist (cerebral thermopooling). Thus, the likelihood of some areas of the brain being hyperthermic (which is known to worsen outcome) is reduced.

Side-effects of induced hypothermia

Cardiovascular system

A hypothermia-induced increase in catecholamines leads to an increase in cardiac output and oxygen demand. With further hypothermia, decreases in heart rate and the slowing of metabolism reduce cardiac afterload and oxygen demand. Therefore, mild hypothermia causes a decrease in cardiac output. Systemic vascular resistance is increased and central venous pressure increases. Thus, mean arterial pressure is usually maintained. ECG changes include increased PR interval, widening of the QRS complex, and the appearance of the Osborne or ‘J wave’ (a notch on the downstroke of the QRS complex). Arrhythmias

Key points

Induced hypothermia aims to avoid the complications associated with hypothermia.

It is principally used in comatose cardiac arrest survivors, head injury, and neonatal encephalopathy.

The mechanism of action is thought to be mediated by prevention of cerebral reperfusion injury.

The main problems associated with its use are diuresis, electrolyte imbalance and immunosuppression.

The International Liaison Committee on Resuscitation recommend that it is used for comatose survivors of VF, out-of-hospital cardiac arrests.

Cerebral hypothermia can safely improve intact survival in term infants with neonatal encephalopathy.
are rare >30°C. Below this temperature, risks are greatly increased and AF is usually followed by refractory VF when the temperature is decreased to <28°C.

**Respiratory system**

The decrease in metabolic rate at 33°C means that ventilator tidal volumes will need reducing to maintain PaCO₂ in the normal range. There is a higher incidence of pneumonia in hypothermic patients. Some units use selective gut decontamination which seems to minimize this risk.

**Infection and gastrointestinal function**

Induced hypothermia impairs immune function; nosocomial pneumonia will occur in over half of patients who are hypothermic for >7 days. Wound healing may be delayed and excellent nursing care is required to avoid the development of bed sores. However, with induced hypothermia for <24 h, pneumonias and bed sores are uncommon. The risk of infection is compounded by poor glycaemic control. An important side-effect is insulin resistance and decreased insulin release. An insulin infusion should be used to bring elevated glucose concentrations under control. Decreased gastrointestinal motility will require prokinetics to avoid delays in enteral feeding. Serum amylase and liver enzymes are frequently raised and a metabolic acidosis also occurs as a result of increase in lactate concentrations and increased production of free fatty acids, ketones and glycerol. On rare occasions, these changes can be severe and pancreatitis can ensue.

**Renal system**

Diuresis and electrolyte disturbance are the two primary concerns when using induced hypothermia. Diuresis results from decreased absorption of solute in the ascending loop of Henle. Intracellular movements of potassium, magnesium, and phosphate during induced hypothermia lead to lowered serum concentrations of these anions and regular measurements and correction (if necessary) must be performed. Maintenance of plasma volume is also critical if damaging periods of hypotension are to be avoided. On re-warming, the extracellular shift of anions may lead to increasing plasma concentrations.

**Acid–base**

As temperature decreases, the solubility of gases in a liquid (e.g., blood) increases. Hypothermia presents a problem in the interpretation of arterial blood gases (ABG) as when the ABG sample is adjusted to compensate for the low temperature, patients appear to have a respiratory alkalosis. There are two ways of interpreting the samples: Without correction (alpha-stat management) or by the addition of CO₂ to normalize pH (pH-stat management). Whether during induced hypothermia the samples should be corrected for temperature is unknown; although, in an animal study on cerebral ischaemia treated with induced hypothermia, pH-stat management proved more favourable. However, alpha-stat management is used throughout hypothermia in cardiopulmonary bypass.

**Haematological**

During prolonged induced hypothermia, bleeding time will be lengthened as a result of a reduction in the number and function of platelets. Platelets may be sequestered by the spleen and liver, and return to the circulation on re-warming. The coagulation cascade may also be impaired, although the direct tests such as prothrombin time (PT) and activated partial thromboplastin time (APTT) may not reflect these changes, as they are performed at 37°C. Therefore, the use of hypothermia in multitrauma patients is controversial as deleterious effects of induced hypothermia on the whole body may outweigh the benefits of neuroprotection. The white cell count also decreases.

**Techniques used for induced hypothermia**

The following techniques can be used to induce hypothermia:

(i) **Antipyretics**, for example, paracetamol.
(ii) **Fans**—may increase infection risk.
(iii) **Ice packs** to the femoral area, major vessels, and armpits. The packs must contain ice plus water to ensure a low temperature. The need changing frequently.
(iv) **Cold fluids**—this has a rapid effect, for example, crystalloid solution 30 ml kg⁻¹at 4°C for more than 30 min. This compensates for anticipated diuresis and helps maintain cerebral perfusion pressure (CPP).
(v) **Water filled blankets or garments** (e.g., Blanketrol)—these are effective with feedback control.
(vi) **Forced cold air**—this is hygienic but has no feedback control. It is very inefficient.
(vii) **Intravascular line**—this is very expensive but control can be excellent. Femoral lines are available.
(viii) **Bypass**—specialist (cardiac) areas only.
(ix) **Cooling caps**—these are mainly used in neonates and infants.

It is imperative to measure core temperature. The alternatives are usually bladder, rectal or nasopharyngeal sites. The disparity between the readings of probes at these sites is negligible. There, is a risk that if a nasopharyngeal probe should become dislodged, a feedback control unit, for example Blanketrol, would commence an inappropriate warming process. Additionally, erroneous nasopharyngeal temperature readings and over-cooling have occurred because of warmed ventilator gases. On our unit, we often measure the temperature in two areas; a bladder probe is usually our primary source. It is worth noting that obese patients are harder to cool, as fat insulates much better than muscle. Elderly patients are easier to cool as they vasoconstrict less readily, and generally have a lower basal metabolic rate.

Sedation is typically required. The vasodilatation this affords will assist the transfer of heat from the core to the periphery and
Clinical applications of induced hypothermia

Cardiac arrest survivors

Out-of-Hospital Cardiac Arrest (OOHCA) is associated with a poor prognosis. An estimated 375 000 people in Europe undergo sudden cardiac arrest annually, making it a major cause of unexpected death in the developed world. If a return of spontaneous circulation (ROSC) is achieved, then anoxic neurological injury is an important cause of morbidity and mortality.

Currently, the treatment of these patients is largely supportive. Two randomized controlled studies have shown that induced hypothermia leads to a markedly more favourable neurological outcome compared with the groups treated without the use of hypothermia.\(^2,3\) In the Hypothermia after Cardiac Arrest (HACA) study, 275 adult patients, who had suffered a witnessed OOHCA with \(<15\) min before professional CPR, were cooled on average 105 min after ROSC. Target temperatures of \(32–34^\circ C\) were reached after approximately \(8\) h and maintained for \(24\) h followed by passive rewarming for more than \(8\) h. The results are shown in Figure 1. The International Liaison Committee on Resuscitation (ILCOR) has since stated, ‘Unconscious adult patients with spontaneous circulation after OOHCA should be cooled to \(32–34^\circ C\) for \(12–24\) h when the initial rhythm was VF’ and that ‘such cooling may also be beneficial for other rhythms or in-hospital cardiac arrest.’\(^4\)

An Australian intensive care unit, where a second trial\(^3\) showed similar benefits of hypothermia after OOHCA, used the following protocol once a patient was to be cooled after cardiac arrest:

The patient (if not already) should be intubated and mechanically ventilated, maintaining a \(\text{PO}_2 > 13.0\ kPa (100\ mm\ Hg)\) and \(\text{PCO}_2\) approximately \(5.3\ kPa (40\ mm\ Hg)\). Mean arterial pressure is maintained between \(90\) and \(100\ mm\ Hg\) using inotropes or vasodilators if necessary. Core temperature is measured using a bladder catheter with a thermistor as soon as practical. Once these measures have been achieved, hypothermia is induced as quickly as possible using ice packs and cold fluid. (Induced hypothermia appears to be efficacious even if delayed for \(4–6\) h. The aim is to achieve a temperature of \(33^\circ C\) within \(4\) h of ROSC. Adequate sedation and muscle relaxation must be provided so that shivering is completely prevented, thus reducing oxygen demand and preventing re-warming.

In the critical care environment, cooling is best continued using a cooling mattress such as the Blanketrol (Cincinnati Sub Zero, OH, USA). This is a water cooled blanket system that measures the core temperature from a bladder probe and aims to match this with a previously entered set point, in this case \(33^\circ C\). The patient can then be cooled with minimum risk of any overshoot of temperature. The temperature is maintained at \(33^\circ C\) for \(12\) h before re-warming is commenced. With this short duration of hypothermia and the relatively small drop in temperature, most hypothermia-induced side-effects do not occur. The principal problems are electrolyte disturbance requiring correction, and diuresis requiring volume replacement.

When the period of hypothermia is completed, re-warming is commenced actively or passively. If active, and a Blanketrol system has been used, the set-point temperature is simply adjusted to \(37^\circ C\) and the machine warms the patient. It is important to remember that the potassium ions which have been driven intracellularly by hypothermia will now become extracellular. If a potassium infusion has been used to increase the serum potassium concentrations, there is a risk of hyperkalaemia during re-warming. Vigorous measures to prevent shivering must be taken at all times to avoid increasing oxygen demand in an already potentially ischaemic myocardium.

Traumatic head injuries

Over the last \(20\) yr, the outcome of patients with severe head injury has steadily improved because of a combination of factors. These include more rapid evacuation of casualties to Accident and Emergency departments, prevention of hypoxaemia and hypotension; improved and more readily available imaging, and surgical intervention. Additionally, the focus is on the maintenance of adequate CPP because of the widespread adoption of ICP measurement.

However, mortality and morbidity after severe head injury remains high. The use of hypothermia for head trauma remains controversial despite its continued use in many centres. A large multicentre study in 2001 showed no benefit from hypothermia in traumatic brain injury.\(^5\) There were, however, more complications in the hypothermic group and the trial may have suffered from the fact that some centres recruited very small numbers of patients with a good neurological outcome and the mortality at \(6\) months in the normothermic and hypothermic groups of the HACA study. The light grey columns represent the number needed to treat (NNT) to have one more patient with a good outcome or to prevent one patient dying at \(6\) months.

Trumatic head injuries
Table 1: Glasgow outcome score (GOS) after neurological injury

<table>
<thead>
<tr>
<th>GOS</th>
<th>Definition</th>
<th>Description</th>
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<tbody>
<tr>
<td>5</td>
<td>Good recovery</td>
<td>Resumption of normal life despite minor deficits.</td>
</tr>
<tr>
<td>4</td>
<td>Moderate disability</td>
<td>Disabled but independent. Can work in a sheltered setting.</td>
</tr>
<tr>
<td>3</td>
<td>Severe disability</td>
<td>Severe disability. Can work in a sheltered setting.</td>
</tr>
<tr>
<td>2</td>
<td>Persistent vegetative state</td>
<td>Persistent vegetative state. Dependent for daily support.</td>
</tr>
<tr>
<td>1</td>
<td>Death</td>
<td>Nonsurvival</td>
</tr>
</tbody>
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Table 2: Results from Polderman et al.

<table>
<thead>
<tr>
<th></th>
<th>Hypothermia</th>
<th>Normothermia</th>
</tr>
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<tbody>
<tr>
<td>ICP before cooling (mm Hg)</td>
<td>37</td>
<td>&lt;20</td>
</tr>
<tr>
<td>ICP during cooling (mm Hg)</td>
<td>14</td>
<td>&lt;20</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>62.5%</td>
<td>72.2%</td>
</tr>
<tr>
<td>Good/excellent GOS</td>
<td>15.6%</td>
<td>9.7%</td>
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Clinical applications of induced hypothermia

patients. Some of the problems of hypothermia, such as reduced CPP and electrolyte imbalance may have been under-treated. A subset of younger patients with a Glasgow Coma Score of 4–7 who were already cold on admission, and were then kept cold, did seem to have a better outcome.

A Cochrane Review also did not recommend the use of induced hypothermia on the basis of published papers. However, their conclusions did not include data from two recent trials that have both shown benefits from cooling after traumatic brain injury.5,7 In the first study,6 Polderman and colleagues used hypothermia as a last effort to reduce ICP in patients where all other methods had failed. They were able to demonstrate a reduction in ICP attributable to hypothermia. In this treatment protocol, invasive arterial, central venous pressure and ICP monitoring were utilized. Bench side electrolyte measurement allowed for the tight control of fluid and electrolyte imbalance. CPP was maintained at an acceptable level. All standard methods were used to reduce the ICP to <20 mm Hg. This involved a step-wise progression from simple head tilting to the use of mannitol, neuromuscular blocking agents and barbiturates. If the ICP remained >20 mm Hg, hypothermia was induced in the study group. The target temperature of 32–34°C was maintained for 24 h. After this period, the temperature was increased slowly by 1°C per 12 h and, if ICP remained low, warming was continued; otherwise, cooling was again instituted. The average duration of hypothermia was nearly 5 days. This longer period of cooling may explain the difference in final outcome. The only complication reported was an increase in the incidence of chest infections. At 6 months, blinded clinicians scored the patients according to their neurological wellbeing by using the Glasgow Outcome Score (Table 1). The results (Table 2) are especially significant as there was a bias against the hypothermia group as these were the patients in whom elevated ICP was refractory to other treatment methods.

In the study reported by Zhi and colleagues involving 396 patients who had a longer period of induced hypothermia, similar improvements were seen.7

Newborn hypoxic–ischaemic encephalopathy

The concept of brain protection by hypothermia has been extended to the treatment of the newborn. In a randomized, multi-centre, controlled trial of delayed cerebral hypothermia for neonatal encephalopathy, 234 infants were randomized to hypothermia or normothermia.9 The infants had clinically defined moderate to severe neonatal encephalopathy plus abnormal amplitude integrated electroencephalography (aEEG). The results suggested a protective effect of the hypothermia; although there was no effect on those with the most abnormal aEEG. In those with an intermediate aEEG, a significant reduction in adverse outcome was observed with no increase in complications.

Cooling was achieved by using a head cap with circulating water at 10°C, a process known as selective head cooling (SHC). Rectal temperature was maintained at 34–35°C. SHC recognizes the fact that brain and core temperature may differ as a result of surgery, anaesthesia, or pathology. Brain temperature in the patient under hypothermic management appears to be approximately 1°C greater than axillary temperature, emphasizing the potential advantage of measuring brain temperature directly and (as in this study) attempting to directly cool the brain.

Neurosurgery

There is no clear answer as to whether induced hypothermia should be used as a general method of neuroprotection. Despite this, a recent survey of members of the Neuroanaesthesia Society of Great Britain showed that 58% attempted to cool patients during cerebral aneurysm surgery. Additional monitoring during hypothermia, such as the bispectral index (BIS) and burst suppression ratio, are useful tools to allow depth of anaesthesia coupled with hypothermia to be monitored. BIS monitors have been shown to correlate well with a full channel electroencephalogram (EEG). A recent multicentre trial (IHAST2) showed no benefit of cooling patients to 33°C intraoperatively for clipping of intracranial aneurysms after sub-arachnoid haemorrhage. All patients (n = 1001) underwent good grade aneurysm clippings. It is difficult to tell if complicated cases involving prolonged temporary clipping or rupture would still benefit from some degree of hypothermia. It is likely that its routine use in uncomplicated aneurysm surgery will be abandoned.

Cerebrovascular accident (stroke)

In ischaemic stroke, neuroprotective agents have not shown great promise. However, in their study of 396 patients, Kammersgaard and colleagues were able to show that the admission body temperature seems to be a major determinant for long-term mortality after stroke.10 They concluded that ‘hypothermic therapy in the early stage, in which body temperature is kept low for a longer
period after stroke onset, could be a long-lasting neuroprotective measure’. Since then, there have been numerous animal models and some preliminary studies but no conclusive results. The Cochrane review stated that further trials were indicated. If induced hypothermia was found to positively effect upon the outcome of stroke patients, the impact on critical care resources would be significant.

Other areas

Raised ICP seen in hepatic encephalopathy has been controlled using hypothermia; other reported situations include ARDS and spinal cord protection for aortic surgery. The use of hypothermia in cardiac surgery has been noted earlier; it has not been covered in this review.

References


Further reading


Please see multiple choice questions 17–20.