Journal of Paediatric Respirology and Critical Care

Therapeutic hypothermia in children: to cool or not to cool?

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Introduction

Hypothermia has been used for various reasons in the practice of medicine for at least a couple of centuries. In 1970s and 1980s therapeutic hypothermia (TH) was used to treat cerebral oedema in children and adolescents after cardiac arrest caused by drowning.[1] Bohn and Biggart later reported increased risk of death, neutropenia and sepsis with hypothermia therapy. This led to abandonment of this therapy.[2,3] Potential limitations of these studies were that historical controls were used, that the patients were cooled to temperature that were too low (30-33°C), that the duration of hypothermia was too long (days) and that the therapy was combined with barbiturate coma, which had adverse effects that added to those of hypothermia.[2]

It was not until Bernard and associates showed improved outcome without major complications in out-of hospital cardiac arrest victims treated with hypothermia that interest in this aspect was aroused again.[4]

Animal models

A lot of evidence underlying clinical use of hypothermia and its neuro-protective mechanisms come from animal models. There are two basic categories of ischaemia models, global ischaemic model and focal ischaemic model, closely representing the clinical situation of cardiac arrest or near drowning and stroke respectively. In global ischaemia model, there is a transient 5-30 minutes complete or near complete global lack of blood flow. If flow does not resume within 30 minutes, widespread necrosis ensues and tissue functional recovery is not possible. If reperfusion occurs within 30 minutes, there is selective neuronal death due to difference in sensitivity to ischaemia between different types of neurons and brain regions.[5]

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In focal model, there is localised, more prolonged (60-90 minutes) ischaemic period from e.g. a single vessel occlusion. Pan necrosis will ensue in a central core region closest to the occluded vessel if re-perfusion is not established within 60 minutes. The hypo-perfused regions surrounding this central core region, called penumbra, though at risk of dying, is salvageable with increased perfusion and/or other interventions. If no intervention occurs, the tissue at risk will begin to die within 3-4 hours of reperfusion. If occlusion lasts 6 hours the penumbra evolves to become core. At normothermia, infarction is essentially complete by 24 hours. Ischaemic oedema peaks at approximately 48 hours after injury.[5]

Most animal studies on effects of hypothermia on global or focal neurological injury have reported protective effects provided that hypothermia was applied quickly enough.[6-8] It has been shown that the earlier TH is initiated, the earlier the target temperature is reached and the greater chance of favourable outcome.[9,10] Though reproducing similar results in clinical trials is difficult for various reasons, this provides important clues on how hypothermia works and how it should be applied.

Therapeutic hypothermia in adults

Post-cardiac arrest

In 2002, the hypothermia after Cardiac Arrest Study Group showed that mild hypothermia (32-34°C) when applied to unconscious out-of hospital cardiac arrest adult patients with return of spontaneous circulation (ROSC) provide significant improvement in functional recovery at hospital discharge (55% vs 39%) and lower 6-month mortality rate when compared with patients who were not cooled (41% vs 55%).[11] The number needed to treat (NNT=6) is very low and is comparable to other important emergent treatment such as cardiac catheterization for acute coronary syndrome.[12] Bernard examined the end point of survival to hospital discharge

(good outcome) in 77 patients and demonstrated 49% in the hypothermia group vs 26 % in the normo-thermia group.[13]

American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care made the following recommendations in 2005:

- Unconscious adult patients with ROSC after out-of hospital cardiac arrest should be cooled to 32-34°C for 12-24 hours when initial rhythm was ventricular fibrillation (class IIa)
- Similar therapy may be beneficial for patients with non-VF arrest out-of hospital or with in-hospital arrest (class IIb)
- Hemodynamically stable patients with spontaneous mild hypothermia (>33°C) after resuscitation from cardiac arrest should not be actively re-warmed[14]

Similar recommendations were also made by International Liaison Committee (2003) on Resuscitation and the European Resuscitation Council (2005).[15,16]

Post severe traumatic brain injury

Mild hypothermia has been shown to be effective in traumatic brain injury (TBI) with high intracranial pressure in adults[17] but no benefits for patients with TBI with normal ICP.[18] In a systematic review and meta-analysis published by Brain Trauma Foundation/ American Association Neurol Surgeons (BTF/AANS) in 2008, 8 eligible trials on patients who sustained severe traumatic brain injury were selected. It was shown that there was greater reduction in mortality risk and favourable neurological outcome was much more common when hypothermia was maintained more than 48 hours. However, HT was of significant benefit only to patients who were not enrolled in trials in which barbiturate was part of the standard elevated intracranial pressure (ICP) management protocol. They also conclude that potential benefits is likely to be offset by significant increased risk of pneumonia.[19] Level III recommendation for optimal and cautious use of hypothermia for adult with traumatic brain injury was put up by BTF/AANS guidelines task force in 2008.[19] However, they also recommended ICP measurement guidance, slow (over 24 hours) re-warming and prevention of fever in first 24-48 hours.[19]

Other types of brain injury

Currently there is no clinical evidence regarding the role of therapeutic hypothermia in other situations like patients with acute stroke and traumatic spinal cord. However, there is strong evidence that fever is correlated with poor clinical outcomes in acute stroke.[20]

Therapeutic hypothermia in neonates

A number of recent randomised controlled trials on the use of TH in neonates with hypoxic-ischaemic encephalopathy have shown reassuring results regarding safety and applicability of this modality of treatment.[21,22] Jacobs, in a Cochrane review found that TH results in reduction in the combined outcome of mortality or major neuro-developmental disability at age 18-month (RR 0.76;95% CI 0.65-0.89) with a number needed to treat to be 7 (95% CI 4-14).[23] They also found a significant increase in thrombocytopenia although it was not clinically significant.[23] The International Liaison Committee on Resuscitation (ILCOR) advocates the use of therapeutic hypothermia following perinatal asphyxia related cardiac arrest in term newborn.[24]

Is therapeutic hypothermia useful in children outside the neonatal age group?

Post-cardiac arrest

Paediatric data on effect of this treatment modality after cardiac arrest are limited. However, support for this treatment is extrapolated from the adult and neonatal studies. Recommendation similar to that for adults that therapeutic hypothermia may be beneficial and should be considered in patients who has ROSC but remain comatosed after cardiac arrest have been made by ILCOR (2006),[25] ERC (2005)[26] and AHA (2005).[27]

The range of hypothermia is 32-34°C for 12-24 hours. Following a period of mild hypothermia, slow re-warming is to be done at 0.25-0.5 C/h (ERC). It is also recommended that the successfully resuscitated child with hypothermia and ROSC should not be actively re-warmed unless the core temperature is below 32°C.[26]

Traumatic brain injury

A recent large international multi-centre RCT study by the Hypothermia Paediatric Head Injury Trial Investigator & Canadian Critical Care Trials Group on patients with severe TBI showed unfavourbale outcome both in terms of death, complications and neuro-developmental performance at 6 months.[28] There are much less clinical studies on use of TH in other types of brain injury in children.

Practical aspect for cooling

Timing and therapeutic window for therapeutic hypothermia

As discussed earlier, experimental data suggests that there is a window period for early initiation of hypothermia. Although there is no human studies data, animal studies by Safar demonstrated beneficial effects of mild to moderate TH induced very early after survival from cardiac arrest.[6-8] Experimental data suggests that cooling should be initiated as soon as possible but should not be withheld even if delays of up to 8 hours occur.[5] Cooling should be performed rapidly to achieve maximum effectiveness.

Patient preparation

Do not actively re-warm patients who are spontaneously hypothermic. Shivering is an important unwanted physiological change during hypothermia. It increases cellular metabolism, oxygen consumption and hence decreases the effectiveness of TH. It also causes patient discomfort. Use of sedation and pain relief (e.g. pethidine is said to decrease shivering threshold)[29] and neuro-muscular blockade is often necessary to manage shivering.

Monitoring of temperature

Induced hypothermia at 32-34°C is recommended for most therapeutic purposes.[15] It is vital to have reliable continuous temperature measurement to achieve tight control of temperature with minimal variations and to avoid undesirable adverse effect of over-cooling. Temperature monitoring can be done with a variety of probes, namely rectal, tympanic, oesophageal, bladder, vaginal or pulmonary artery catheter. Tympanic temperature shows good correlation with intracranial temperature, is non-invasive and easily applied although the presence of ear wax can affect the reading.[30] Cooling of face is to be avoided if TM is used as reading may be affected. Since rectal temperature does not correlate well with intracranial temperature and rectal reading can be inaccurate due to faecal insulation, rectal probe is less useful.

Methods for cooling (Table 1)

There are various methods of cooling. Surface cooling is non-invasive and simple to use. Examples include cooling blankets with either circulating cold water or cold air, or even less sophisticated methods like ice packs.[31] This method takes longer time to reduce body temperature, e.g. 2-8 hours. Newer surface cooling methods include adhesive hydrogel-coated pads that circulate temperature controlled water under negative pressure. In infants, selective induction of hypothermia of surface of head and neck may be achieved by cooling helmets or caps.

Invasive cooling methods like infusion of cold intravenous fluids, extra-corporal circulation of cooled blood, ice water nasal and rectal lavage or cold peritoneal lavage. Bernard et al[32] showed that cooling of core temperature from 35.5 to 33.8°C within 30 minutes can be achieved using infusion of cold intravenous fluid without adverse consequence. There are also intravascular catheters that consist of 2-3 balloons filled with temperature controlled saline to achieve endovascular cooling via central veins. The safety profile of these device used for long term cooling (>24 hours) have yet to be established.

Table 1. Cooling techniques

Non-invasive	Invasive
Cooling blankets	Infusion cold IV fluids
Water-circulating	
Air-filled	
Ice packs	Retrograde jugular vein flush
Caps or helmets	Extracorporeal circulating cooled blood
Cold water immersion	Lavage (nasal, nasogastric, rectal, peritoneal)
Hydrogel-coated cooling pads	Intraventricular cerebral hypothermia

Potential adverse effects (Table 2)

Hypothermia therapy seems to be relatively safe when applied at temperature more than 32°C for short duration (24 hours). Induction of hypothermia causes a large number of physiological changes in multiple systems in the body. Physiological effects and adverse effects depend on the degree of hypothermia. For hypothermia to be successful, awareness of these physiological effects and pathophysiological mechanisms is of key importance. Some of the physiological changes may not cause significant deterioration in patients and do not require treatment or premature stopping of hypothermia.

The main concern has been the development of arrhythmias at temperatures below 32°C.[33] This risk is further increased by the tendency for electrolyte disturbance e.g. decreased sodium/potassium/magnesium/phospohate. Great care must be taken when cooling because patient's temperature can easily overshoot below 32°C unless core temperature is closely monitored.

Mild adverse effects occur at clinically relevant temperature and durations of hypothermia, including bradycardia, lower cardiac out-put and hypotension, especially during re-warming. Pancreatic, metabolic and renal abnormalities are also seen. Mild coagulopathy with elevation of prothrombin time and partial thromboplastin time and lower platelet count has been reported.[34] There is a risk of impaired immune function with associated risk of pneumonia and sepsis.[35]

Controlled re-warming

Re-warming of patient is usually begun 12-24 hours after the initiation of cooling. The re-warming phase may be the most critical period. As constricted peripheral vascular bed starts to dilate, hypotension may ensue. It is recommended that rewarming to be done slowly at a temperature of 0.25-0.5 C/hr (ERC) to target 36°C with close monitoring of blood pressure. During induction of hypothermia, potassium is shifted into the cells. There is risk of life threatening hyperkalaemia during re-warming when potassium move out of the cells. Existing intravenous potassium infusion may need to be stopped before re-warming starts and close watch for hyperkalaemia is necessary.[36] Continue sedation and paralysis until the patient's temperature reaches 35°C to continue suppression of shivering.[36]

Conclusion

Evidence from animal models, human adults with cardiac arrest and newborn with hypoxic – ischaemic encephalopathy suggests neuroprotective effect of therapeutic hypothermia (TH). The American Heart Association guidelines, ERC, ILCOR recommend that TH should be considered in children after cardiac arrest. No conclusive data are available for other clinical situation. There are various cooling methods, some of which are non-invasive and easily applied. Meticulous monitoring of body temperature, homeostasis and laboratory tests results are important as there are risks of over-cooling and other adverse effects, including

Table 2. Potential side effects of hypothermia

Frequency/degree or risk	Effect
High risk	Coagulopathy
	Thrombocytopenia, leucopenia
	Electrolytes disturbance (loss of K, Ca, Mg, P) – may be arrhythmia inducing
	Hypovolaemia
	Elevated serum amylase
	Changes in drug effect and drug metabolism
	Insulin resistance
Low risk	Manifest bleeding ,severe coagulation disorders
	Airway/wound infections
	Wound healing
	Myocardial ischaemia
Rare	Intracranial bleeding
	Manifest pancreatitis

arrhythmia, coagulopathy and immune suppression. The successful application of hypothermia requires strict compliance with protocols, vigilance by the medical and nursing staff.

Further studies will be required before a strong recommendation can be made to the hypothermia therapy in children with cardiac arrest and other types of brain injury.

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