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Review Article

Therapeutic Hypothermia

Abstract

Therapeutic hypothermia has been advocated for neuroprotection in cardiac arrest-induced encephalopathy, neonatal hypoxic-ischemic encephalopathy, traumatic brain injury, stroke, hepatic encephalopathy, and spinal cord injury, and as an adjunct to certain surgical procedures. In this review, we address physiological mechanism of hypothermia to mitigate neurological injury, the trials that have been performed for each of these indications, the strength of the evidence to support treatment with mild/moderate hypothermia. Evidence is strongest for prehospital cardiac arrest and neonatal hypoxic-ischemic encephalopathy. For traumatic brain injury, a recent meta-analysis suggests that cooling may increase the likelihood of a good outcome, but does not change mortality rates. For many of the other indications, such as stroke and spinal cord injury, trials are ongoing, but the data is insufficient to recommend routine use of hypothermia at this time. Although induced hypothermia appears to be a highly promising treatment, it should be emphasized that it is associated with a number of potentially serious side effects, which may negate some or all of its potential benefits. Prevention and/or early treatment of these complications are the key to successful use of hypothermia in clinical practice.

Introduction

Cardiac arrest is sudden circulatory standstill and is a common cause of death. Mortality ranges from 65-95% for out of hospital cardiac arrests and from 40- 50% for witnessed in- hospital arrests. Survivors have a high risk of significant neurological injury and only 10-20% are discharged with no significant neurological deficit [1]. Cerebral damage occurs during the period of cardiac arrest due to cerebral ischaemia. Cerebral ischemia may also result from other conditions like birth asphyxia, stroke, and traumatic brain injury resulting in neurological injury. The main reason for use of therapeutic hypothermia [TH] is to protect the brain against irreversible hypoxic damage and hence, to achieve better neurological outcomes in these patients.

The first clinical use of therapeutic hypothermia was first reported after cardiac arrest in 1958 [2], but with inconclusive results. Even Peter Safar championed hypothermia [3] for years but it generally laid dormant until the 1990s probably because of difficulties in the use of moderate hypothermia [28^{0}C-32^{0}C]. Only some surgical procedures, primary cardiac and neurosurgical, used hypothermia for conservation of brain tissue and decreasing cerebral metabolic oxygen rate [CMRO2]. The benefits with moderate hypothermia <30°C were limited owing to significant side effects like arrhythmias, infections, and coagulation problems and the practice was restricted due to the need for cardiopulmonary bypass devices to achieve it. Clinical trials in the late 1980s and 1990s, reported brain damage mitigating effect and safety of mild hypothermia [32^{0}C-35^{0}C] [4]. Two landmark prospective randomized multicenter studies published in 2002 [5,6] and subsequent large clinical trials, have demonstrated improved survival and neurological outcomes with induction of TH. This resulted in its inclusion of mild TH in the Guidelines for Resuscitation from 2005[7] leading to its widespread use. It has been used to provide neuroprotection in survivors of cardiac arrest, neonatal hypoxic encephalopathy, traumatic brain injury, stroke, and various other disorders. The clinical use of TH is likely to increase in the near future; thus, anesthesiologists should have knowledge regarding the clinical applications of TH.

The aim of this review was to describe the evidence for the use of therapeutic hypothermia in clinical practice. The impact of this therapy on outcome and methods for practice of hypothermia will be included in the review. A formal literature search was conducted using PubMed and Cochrane databases, to identify suitable original papers, meta-analysis and reviews. The search headings included the text words: Cerebral ischemia and hypothermia, therapeutic hypothermia and cardiac arrest and resuscitation, traumatic brain injury, neonatal hypoxic encephalopathy, cooling methods, outcome. The additional source of data was a hand search of references from relevant articles.

Definition

By definition, hypothermia is a body temperature less than 36°C and it is divided into three stages: mild hypothermia, when the body temperature is between 35°C-32°C, moderate hypothermia when the body temperature is between 32°C and 30°C, and deep hypothermia when the body temperature is less than 30°C. Therapeutic hypothermia is defined as a core temperature ≤ 35°C induced deliberately by artificial cooling, which is used to prevent or attenuate various forms of neurological injury [8].

Mechanisms underlying neuroprotective effects of Hypothermia

Cerebral ischemia and subsequent reperfusion injury cause enormous biochemical, structural, and functional insults, which in a complex interrelated process leads to progressive cell destruction, neuronal apoptosis, and death [9]. Hypothermia has been shown to attenuate or ameliorate many of these deleterious temperature-sensitive mechanisms, thereby contributing to protection of the brain [10]. Many of the mechanisms underlying hypothermia's effects

have been derived from animal experiments, although many were subsequently confirmed in clinical studies.

Many studies have shown that hypothermia can prevent cell injury from apoptosis [11,12] and prevention of mitochondrial dysfunction [13,14]. The key destructive processes, such as calcium influx [15], accumulation of glutamate [16], are also blocked by hypothermia. Hypothermia suppresses ischemia-induced inflammatory reactions and release of pro-inflammatory cytokines [17-19]. It mitigates reperfusion injury by reduction in lipid peroxidation and production of leukotrienes, nitric oxide [20] and free radicals [21,22]. These processes continue to last for hours to days after injury. Potentially, this would provide a significant time window for neuroprotective effects of therapeutic interventions such as hypothermia.

Current clinical applications of therapeutic hypothermia

The last decade has seen an overwhelming evidence for mild therapeutic hypothermia in various clinical situations. The evidence is discussed below and summarized in Table 1.

Cardiopulmonary resuscitation [CPR]

Rationale: Neurological injury and cardiovascular instability are the major determinants of survival after cardiac arrest [23]. Hypothermia is a helpful therapeutic approach for protection of the brain and other organs, in patients who remain comatose (usually defined as a lack of meaningful response to verbal commands) after return of spontaneous circulation (ROSC).

Trials and Evidence: Two landmark randomized controlled clinical trials published in early in 2002, the Hypothermia After Cardiac Arrest [HACA] trial [24], and Australian study [6,24]. Both trials concluded that mild therapeutic hypothermia after successfully resuscitated cardiac arrest due to ventricular fibrillation increased the rate of a favorable neurological outcome and reduced mortality [6,24]. Subsequently other randomized clinical trials and studies with historical controls have also shown the beneficial effects of hypothermia for comatose survivors of ventricular fibrillation (VF) cardiac arrest [25-30]. The meta-analysis of these studies in the Cochrane systematic review [31], concluded that, with conventional cooling methods, patients in the hypothermia group were more likely to reach cerebral performance categories score (CPC) of one or two and were more likely to survive to hospital discharge compared to standard post-resuscitation care. There was no significant difference in reported adverse events between hypothermia and control across all studies. Class-I evidence supports the use of hypothermia in patients unresponsive to verbal commands following CPR with. witnessed arrest, brief interval (15 min) until arrival of ambulance, VF, or VT upon arrival of ambulance, ROSC within 60 min and no refractory cardiac shock or persistent hypoxia [32]. Much less data is available for other categories of patients such as those with asystole or pulseless electrical activity (PEA) upon arrival of the ambulance. The results are inconclusive with some reporting the trend was toward good outcome. (Class-III evidence) [33-35] and others not supportive of its role [36-38]. A retrospective historical control study of TH mild in-hospital cardiac arrest showed no difference in neurological outcome. However, the arrest rhythms were predominantly non-shockable [39]. The effectiveness of TH in pediatric CPR is neither supported nor refuted. Randomized controlled trial is ongoing to evaluate the benefits and harms of hypothermia therapy after pediatric cardiac arrest [40,41].

Controversies exist regarding the most efficient method of cooling [27,42], timing [43-45], duration and target temperature. Predictors of good neurological outcome included arrest-to-first cardiopulmonary resuscitation attempt interval </=5 min, ventricular fibrillation or ventricular tachycardia in the first monitored rhythm, absence of re-arrest before leaving the emergency department, arrest-to-return of spontaneous circulation interval </=30 min and recovery of pupillary light reflex [46]. The clinical predictors of survival in patients treated with TH following cardiac arrest were VF on presentation (OR 14.9 p=0.002), pre-cardiac arrest aspirin use (OR 9.7 p=0.02), ROSC <20min (OR 9.4 p=0.003), absence of coronary artery disease (CAD) (OR 5.3 p=0.002) and preserved renal function [47].

Recommendation: The 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science have issued recommendations for use

Table 1: Evidence for Clinical Application of TH.

Condition	Level of Evidence	Comments
Cardiopulmonary resuscitation	Class I [32].	Indications ➢ Witnessed arrest, ➢ brief interval [15 min] until arrival of ambulance ➢ VF, or VT upon arrival of ambulance ➢ ROSC within 60 min ➢ No refractory cardiac shock or persistent hypoxia, ➢ Not responsive to verbal commands
Neurotrauma Adult TBI	Class III [60]. Class II [61].	Reduces ICP Class II [b] Decrease mortality and improve rates of good neurologic recovery. Treatment should be commenced as soon as possible after injury A temperature of 32 degrees -34 degrees C.
Pediatric TBI	Class III [40].	Hypothermia initiated early will have a protective effect Can be done safely. .Remains to be definitively tested
Stroke	Class III b [88].	Evidence for severe MCA infarction.
Clipping of Aneurysm	Class III [95].	IHAST2 (Intraoperative Hypothermia for Aneurysm Surgery Trial part 2) Did not improve the neurologic outcome Postoperative bacteremia was higher.
Neonatal Asphyxia	Class I [79,109].	Benefits of cooling on survival and neurodevelopment outweigh the short-term adverse effects

of mild therapeutic hypothermia in survivors of cardiac arrest [7], (Table 2).

Neurotrauma

Rationale: Traumatic brain injury initiates several secondary metabolic processes that can exacerbate the primary injury. Hypothermia may limit some of these deleterious metabolic responses [48].

Trials and evidence: Results from animal experiments overwhelmingly support the concept of a protective role for hypothermia in traumatic brain injury (TBI) [49]; however, clinical trials have provided conflicting results [50-55]. Although the early large multicenter randomized controlled trial (RCT) [53,56,57], did not demonstrate an overall benefit of hypothermia in severe TBI, subsequent clinical trial data have suggested that systemic methods of inducing hypothermia provide effective control of intracranial pressure (ICP) and cerebral perfusion pressure, as well as improvements in neurological outcome [58,59]. Positive effects on survival and neurological outcome have been achieved only in tertiary referral centers with experience in use of hypothermia, using ICP to guide [60] The recently published meta-analysis supports its usage [61,62] (level of evidence: class IIa). Following on single-institution studies, multicenter TBI trial was undertaken- The North American Brain Injury Study: Hypothermia IIR (NABIS:H IIR) trial was terminated for futility as the results did not confirm the utility of hypothermia as a primary neuroprotective strategy in patients with severe traumatic brain injury [63,64].

Despite lack of evidence for neurological outcome, Therapeutic hypothermia is an effective treatment for control of intracranial hypertension [65-67]. A large clinical trial is underway to evaluate the effect of hypothermia on intracranial pressure [68,69]. Preliminary randomized clinical trials in pediatric TBI have provided the initial data on safety and efficacy [70-72], though larger, Phase III studies have shown that it does not improve the neurologic outcome and may increase mortality. [73] Several reports mention the use of hypothermia in patients experiencing traumatic spinal cord injury [74], but, currently, no large case series assess the value of this intervention in these individuals.

Recommendation: BTF/AANS guidelines task force has issued a Level III recommendation for optional and cautious use of hypothermia for adults with TBI [60]. The available evidence to date supports the use of early prophylactic mild-to-moderate hypothermia in patients with severe TBI [Glasgow Coma Scale score ≤ 8] to decrease mortality and improve rates of good neurologic recovery [61] but larger trials are required for inclusion in standard practice.

Neonatal Asphyxia

Rationale: Hypoxic-ischemic brain injury and hypoxic-ischemic encephalopathy (HIE]) remain a serious problem for both preterm and term neonates with the spectrum of injury ranging from neuronal injury to encephalopathy and death. Given that there is currently no other clinically proven treatment, introduction of TH may be beneficial.

Levels of evidence: Hypoxia ischaemia remains a significant cause of neonatal mortality and morbidity (Level 2c evidence). The trials of hypothermic neural rescue therapy for infants with neonatal encephalopathy that have recently been reported suggest that either selective head cooling [75] or total body cooling [76-78] administered within 6 hours of birth reduces the incidence of death or moderate/severe disability at 12 to 22 months . Studies have shown that there were no serious adverse effects of hypothermia; side effects were similar to those seen in adults and were reversible with re-warming (Level 1a evidence) There is evidence from the eight randomized controlled trials included in Cochrane review [79] and other meta-analysis [80-82] shows that TH is beneficial to term newborns with HIE. (Level 1 evidence) Further trials to determine the appropriate method of providing TH, including comparison of whole body with selective head cooling with mild systemic hypothermia, are required.

Recommendation: The International Liaison Committee on Resuscitation (ILCOR) supports the use of TH following perinatal asphyxia-related cardiac arrest in term newborns with HIE. Cooling reduces mortality without increasing major disability in survivors. Hypothermia to between 33^0C and 34^0C initiated as soon as possible after delivery reduces mortality and disability in babies with HIE (Level 1a evidence).

Stroke

Rationale: The penumbra zone, which is not yet irreversibly damaged, increases outward with time, and in theory this zone can be salvaged as long it has not become necrotic; thus, in theory some benefit could be derived from cooling.

Evidence and recommendations: There is overwhelming evidence from animal studies showing benefits TH in stroke. Only a few small pilot studies have evaluated hypothermia as a treatment for acute ischemic stroke [83-86] and randomized studies are being undertaken [86,87]. There are no controlled trials of hypothermia for hemorrhagic stroke. Logistic challenges present an important barrier to the widespread evaluation of hypothermia for stroke. The Cochrane Database of Systematic Reviews [88] and the 2007 American Stroke Associations Guidelines [89] consider TH to be level III b evidence for severe middle cerebral artery infarction. No clinical studies have been

Table 2: 2010 AHA guidelines for CPR. Recommendations for Hypothermia.

Recommendation	Level of Evidence
Comatose [ie, lack of meaningful response to verbal commands] adult patients with ROSC after out-of-hospital VF cardiac arrest should be cooled to 32°C to 34°C (89.6°F to 93.2°F) for 12 to 24 hours.	Class I, LOE B
Induced hypothermia also may be considered for comatose adult patients with ROSC after in-hospital cardiac arrest of any initial rhythm or after out-of-hospital cardiac arrest with an initial rhythm of pulseless electric activity or asystole.	Class IIb, LOE B
Active rewarming should be avoided in comatose patients who spontaneously develop a mild degree of hypothermia (>32°C (89.6°F)) after resuscitation from cardiac arrest during the first 48 hours after ROSC.	Class III, LOE C

performed in other categories of stroke patients. Use of hypothermia in stroke should be viewed as experimental and should only be used in the context of clinical trials, in centers with extensive experience in the use of hypothermia [90].

Subarachnoid hemorrhage

No large clinical studies in patients with subarachnoid hemorrhage (SAH) have yet been carried out however few case series demonstrated benefit in patients who failed to respond to conventional therapy. There is class-IV evidence for the use of hypothermia to prevent vasospasms in patients with SAH. Fever in patients with SAH is associated with vasospasms and poor outcome and should be treated symptomatically [91,92].

Intraoperative hypothermia

Rationale: Intraoperative hypothermia is used in neurosurgical procedures, cardiac surgery, and major vascular surgery. Usually, the aim of intraoperative hypothermia is to increase time available for specific surgical procedures, by reducing metabolism and providing protection for the brain and/or the spinal cord during local vascular occlusion or complete circulatory arrest. An important difference between intraoperative hypothermia and other therapeutic applications is that treatment can be initiated before and during the insult. This may be important because protective effects of hypothermia particularly in focal ischemia may be much greater if hypothermia is initiated quickly.

Neurosurgery

The small studies by Karibe et al. [93], and Hindman et al. [94], observed improved CBF in the ipsilateral frontal cortex, lower frequency of neurological deterioration and a greater incidence of long-term good outcomes and concluded that intraoperative hypothermia can reduce severity of ischemia induced by temporary cerebral vessel occlusion. A large prospective multi-center trial, the IHAST2 (Intraoperative Hypothermia for Aneurysm Surgery Trial part 2), on 1001 patients with good-grade patients concluded that mild intraoperative hypothermia did not improve the neurologic outcome after craniotomy [95]. Moreover, postoperative bacteremia was more common in the hypothermia group than in the normothermia group. There was no difference between hypothermic and normothermic patients in the occurrence of cardiovascular events [96].

Vascular surgery and spinal cord protection

Hypothermia is also used intraoperatively to protect the spinal cord and prevent paraplegia during high aortic cross surgery. However, despite the widespread use of hypothermia in aortic arch surgery, relatively few clinical data are available. A small controlled trial comparing the effect of spinal fluid drainage, papavarine, and epidural hypothermia to controls also concluded that hypothermia conferred added protection against neurological injury [97].

Cardiac surgery

Transient cognitive deficits develop in 30–80% of patients undergoing cardiac surgery during the first postoperative month, with deficits persisting in 0–30% of patients. Intraoperative and brief postoperative cooling in patients undergoing cardiopulmonary bypass surgery was shown to reduce cognitive dysfunction [98]. However, some authors failed to demonstrate conclusive benefits of intra- and postoperative hypothermia on cognitive function in elective bypass surgery [99]. It has been hypothesized that these differences may be due to duration of cooling and speed of re-warming

Evidence and recommendations: Although intraoperative hypothermia is widely used, firm evidence from randomized controlled trials is lacking or is conflicting [99]. The evidence supporting use of intraoperative hypothermia for intracerebral aneurysm surgery is class-IIb evidence. For cerebral- and spinal cord protection during thoraco-abdominal aortic aneurysm repair the evidence rates as class-III evidence [95]. The use of mild hypothermia for neuroprotection during cardiac surgery is supported by class-III evidence [99].

Myocardial Infarction

TH has been shown in randomized clinical trials to improve neurologic outcomes following cardiac arrest due to acute myocardial infarction (AMI)Mild TH in combination with primary PCI is feasible and safe in patients resuscitated after cardiac arrest due to acute myocardial infarction [100, 101]. A combination of these therapeutic procedures should be strongly considered as standard therapy in patients after out-of-hospital cardiac arrest due to ST-Segment Elevation Myocardial Infarction (STEMI), [101-103].

Physiological, Metabolic and cellular effects of hypothermia on other systems

Induction of hypothermia causes a large number of adverse effects due to the physiological changes in the circulatory and respiratory systems, coagulation system, drug metabolism, etc whose severity depends on the degree of hypothermia. For the successful use of hypothermia, awareness of these physiological effects and pathophysiological mechanisms is of key importance.

Hypothermia reduces oxygen consumption and carbon dioxide production. The reduction in fat metabolism results in increased glycerol, free fatty acids, ketonic acids, lactate causing metabolic acidosis [104]. This is important for appropriate ventilator adjustments and acid –base balance. There is a rise in the levels of adrenaline, noradrenaline and cortisol which along with reduction in insulin secretion can result in decreased insulin sensitivity and hyperglycemia. Tight glycemic control should be maintained as hyperglycemia can be hazardous in neurological injury [105]. Hypothermia causes reduction in heart rate and cardiac output with increased systemic vascular resistance. Heart rate less than 40 is frequent and is not a cause for concern in the absence of other evidence of hemodynamic instability. The ECG changes include increased PR-interval, widening of QRS-complex, increased QT interval. Osbourne or camel wave are seen. Mild arrhythmias are frequent and with further reduction in temperature there is increased risk of tachyarrhythmias, beginning with atrial fibrillation. If life-threatening dysrhythmia arises and persists, or hemodynamic instability ensues active cooling should be discontinued and the patient rewarmed [106]. Platelet count is decreased with impaired platelet function and also impaired coagulation cascade increasing risk of bleeding. No intervention is required if no active bleeding but cooling should be discontinued if

bleeding present. It also causes reduction in white blood cell count with impaired neutrophil and macrophage function and suppression of pro-inflammatory mediator release resulting in increased risk of infection (mainly pneumonia & wound infections). Early antibiotic therapy improves outcome [107]. Renal tubular dysfunction may ensue causing hypovolemia and electrolyte dysfunction due to loss of K, Mg, P, Ca. Potassium values less than 3.5 mEq/L should be treated while the patient is being cooled. Potassium administration should be stopped once rewarming begins as potassium exits cells in this phase. There can be impairment of bowel function and also hepatic dysfunction. This results in altered clearance of various medications [data available for muscle paralyzers, propofol, fentanyl [108], phenytoin, pentobarbital, verapamil, propanol and volatile anesthetics [reduced clearance], but in all likelihood applies to many other types of medication.

Monitoring of these complications is important as they can result in hazardous outcomes for patients. The failure to demonstrate positive effects of hypothermia in some clinical trials may be partly due to insufficient regard for side effects causing the negation of protective effects.

Practical Aspects of TH

Implementation of hypothermia requires planning, education, and integration of multiple services within an institution.

Patient Selection

Inclusion criteria: Patients who have been shown to benefit from induced hypothermia from the conditions mentioned earlier (Table 1).

Exclusion criteria: Exclusion criteria are in part based on theoretical increases in risk. Patients with recent major surgery within 14 days, systemic infection/sepsis, patients in a coma from other causes (drug intoxication, preexisting coma prior to arrest) known bleeding diathesis or with active ongoing bleeding, pulseless electrical activity (PEA), asystolic, or in-hospital arrest are not suitable candidates for TH. In neonates with HIE, TH may not be beneficial when cooling cannot be initiated within 6 hours of birth, birth weight is < 1800g, there are major congenital abnormalities including: suspected neuromuscular disorders, significant chromosomal abnormalities or life threatening abnormalities of the cardiovascular or respiratory systems infants with severe coagulopathy despite treatment, those requiring inspired oxygen over 80%, infant is 'in extremis' and not expected to survive [79].

Cooling

Treatment goal: The goal is to achieve the target temperature (32-34°C) as quickly as possible. In most cases, this can be achieved within 3-4 hours of initiating cooling.

Cooling must be performed rapidly to achieve maximum effectiveness and should be instituted as early as possible. When possible, hypothermia therapy for patients with out-of-hospital cardiac arrest should be initiated in the emergency department [110], or even on field [111]. Treatment can be continued in the intensive care unit (ICU)Patients who are spontaneously hypothermic should not be actively rewarmed.

Methods of cooling: Various cooling methods are described. External cooling with ice packs cooling blankets or surface heat-exchange device and ice is easy but ineffective. Cold saline infusion can be given via a peripheral line or femoral venous catheter to assist in achieving goal temperature. The infusion is 30 mL/kg of 4°C normal saline over 30 minutes. This is not to be used via a jugular or subclavian line because the safety via this method is not yet known. Endovascular cooling allows most rapid cooling, tightest control of target temperature, and minimization of shivering. Pulmonary edema is a risk during cold saline administration. Selective head cooling devices have been shown to be useful in neonates.

Monitoring

An arterial line should be placed early for blood pressure monitoring as peripheral vasoconstriction will increase the difficulty of placing the line after the patient is cooled. Monitor vital signs and oxygen saturation and place the patient on a continuous cardiac monitor, with particular attention to arrhythmia detection and hypotension. Goal of more than 80 mm Hg is preferred from a cerebral perfusion standpoint. Norepinephrine or Dopamine may be used if required. A continuous core temperature monitor should be used; this provides data to modulate cooling efforts and to avoid overcooling.

Medication

Patient comfort and sedation: Agitation and pain guidelines for the institution should be followed. Parenteral narcotic analgesia can be provided with morphine or fentanyl; sedation can be maintained with agents such as midazolam or propofol [112,113].

Paralysis to prevent shivering: Shivering is uncomfortable, and it generates heat, interfering with the cooling process but may be associated with an increased likelihood of good neurologic outcome as compared to its absence [114]. When using conventional surface cooling, sedation and paralysis with pharmacologic neuromuscular blockade is usually necessary. Many patients can have paralytic agents discontinued once the target core body temperature is achieved.

Supportive therapy: Skin care should be checked every 2-6 hours for thermal injury caused by cold blankets. Nutrition need not be provided to the patient during the initiation, maintenance, or rewarming phases of the therapy.

Controlled rewarming

The goal after rewarming is normothermia [ie, avoidance of hyperthermia]. Rewarming of the patient is begun 24 hours after the initiation of cooling. The rewarming phase may be the most critical, as constricted peripheral vascular beds start to dilate. Peripheral hyperemia may cause hypotension. The literature recommends rewarming slowly at a temperature of 0.3-0.5°C every hour. Rewarming will take approximately 8 hours. The goal is to have the patient warm at about 0.3-0.5°C per hour up to a target of 36°C. The paralytic agent and sedation are maintained until the patient's temperature reaches 35°C. If infusing, discontinue the paralytic agent first. The sedation may be discontinued at the practitioner's discretion. The patient is monitored for hypotension secondary to vasodilatation

related to rewarming. Potassium infusions should be discontinued as hyperkalemia may occur when patients are rewarmed.

Cost-effectiveness and Impact

TH was found to significantly shorten ICU stay and time of mechanical ventilation in survivors after out-of-hospital cardiac arrest [115]. The cost-effectiveness of hypothermia was less than $100,000 per quality-adjusted life year [116]. In 2003 only 13-25 % of cardiac-arrest patients receive TH in the USA. The ILCOR in 2002 and AHA ACLS and ERC guidelines of 2005 have recommended hypothermia after cardiac arrest. There was a Steady increase annually from 2003 majority of units starting in 2007 or 2008. In a survey done in 2008, 47% of responders indicated they had used TH. 40.6% had TH policy in the institution [117]. In 2010, 98.4% were practicing TH and 85.6% were using hypothermia as part of post-cardiac arrest management [118]. The practice of TH in India has not been surveyed.

Conclusion

A large body of evidence suggests that hypothermia can be used to prevent or limit damage to the injured brain and spinal cord, and perhaps the heart, in selected categories of patients. It is important to induce hypothermia as quickly as possible, as protection appears to be greater when cooling is initiated early (although benefits have been reported even when cooling was initiated many hours after injury). The induction of hypothermia will affect every organ in the body and it is important that anesthesiologists are aware of this and are able to distinguish physiological changes from pathophysiological side effects. Implementation of hypothermia requires planning, education, and integration of multiple services within an institution.

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Appendix 1: Summary of Trials on Hypothermia for Cardaic Arrest.

Author /Year	Methods	Results	Conclusion
Bernard Gary et al. [6].	Randomized, controlled trial. Comatose patients after ROSCA from OHCA [VF/VT]. 77 patients-hypothermia [33 degrees C within 2 hours after ROSC for 12hrs] and normothermia.	Good Outcome- Hypothermia-21/ 43 (49%): Normothermia -9/34 (26%) P=0.046). Odds ratio for a good outcome with hypothermia -5.25 (95% C.I. 1.47 to 18.76; P=0.011). No difference in the frequency of adverse events.	Moderate hypothermia appears to improve outcomes.
HACA group [24].	Multicenter, randomized controlled trial Patients resuscitated after cardiac arrest due to ventricular fibrillation Hypothermia-32-340 for 24 hours] or normothermia.	CPC 1 or2- Hypothermia 75/136 (55%): Normothermia 54/137 (39%) (RR, 1.40; 95% C.I. 1.08 to 1.81). Mortality at 6mo- Hypothermia-56/137: Normothermia76/138 (RR-0.74: 95% C.I.-0.58 to 0.95). No difference in complication rate between the two groups.	Therapeutic mild hypothermia increased the rate of a favorable neurologic outcome and reduced mortality.
Belliard G et al. [26].	Historical control [n=36] vs mild hypothermia [n=32 in out-of-hospital cardiac arrest due to VF.	Historical controls [36] vs TH [32]. Survival was significantly higher in the hypothermia group (56% versus 36%).	TH is efficient in significantly improving survival and neurological outcome of out-of-hospital cardiac arrest with VF.
Castrejon S et al. [25].	Randomised controlled trial - control group [28] Hypothermia [41].	Good neurological outcome. At discharge-Hypothermia 18 (43.9%): Control 5 (17.9%) RR=2.46; 95% C.I. 1.11-3.98; P=.029). At 6 months Hypothermia-19 (46.3%): Control 6 (21.4%) (RR=2.16; 95% C.I. 1.05-3.36; P=.038).	Hypothermic treatment after cardiac arrest (VF/VT) helps improve the prognosis.
Holzer et al. [27].	Retrospective cohort study in unselected survivors of cardiac arrest. Endovascular cooling 330C for 24hrs vs standard postresuscitation therapy.	.Survival-Endovascular cooling group- (67/97 patients versus 466/941 patients; odds ratio 2.28, 95% CI, 1.45 to 3.57; P<0.001). Good neurological outcome- Endovascular cooling-51/97 patients (53%) 320/941 (34%): control group (odds ratio 2.15, 95% CI, 1.38 to 3.35; P=0.0003; adjusted odds ratio 2.56, 1.57 to 4.17). No difference in the rate of complications except for bradycardia.	Endovascular cooling improved survival and short-term neurological recovery. Temperature control was effective and safe with this device.
Oddo et al. [34].	Retrospective study, Out-of-hospital cardiac arrest due to VF and non-VF rhythms. therapeutic hypothermia [330 -55 Control 54.	TH beneficial in short duration of cardiac arrest (<30 mins). Cerebral Performance category 1 or 2. VF with TH- 24 of 43 patients [55.8%] Control-. 11 of 43 patients (25.6%] p = .004]. Non VF- outcome poor: With TH - 5of 17 patients of Control - 0 of 14 p = .0.27).	major benefit on patient outcome appeared to be related to the type and the duration of initial cardiac arrest.
Arrich et al. [33].	Multicentre data from European Cardiac Arrest Registry 650 patients from 19 sites.	462 [79%] treated with therapeutic hypothermia irrespective of the presenting rhythm. VF group - Demonstrates a benefit in terms of neurological outcome at 6 months – CPC 1-2:45% in hypothermia group vs. 32% in normothermia group (ARR 13%; NNT = 7.6; P = 0.02). Non-significant increase of favorable outcome in hypothermic patients in Asystole/ PEA groups: 35/124 (28%] in the hypothermic group; 14/73 (19%) in the normothermic group [ARR 9%; NNT = 11.1; P = 0.18).	
Don CW et al. [119].	Retrospective. Total of 491 consecutive adults with OHCA. 204 –before use of TH. 287 during use of TH.	Compared to control pts with VF who received TH had improved survival [odds ratio, 1.71, 95% confidence interval, 0.85-3.46] and had favorable neurologic outcome (odds ratio, 2.62, 95% confidence interval, 1.1-6.27). Benefit was not observed in patients whose initial. rhythm was PEA or asystole.	TH associated with a significant improvement in neurologic outcomes in patients whose initial rhythm was VF, but not in patients with other rhythms.

OHCA-out of Hospital Cardiac Arrest: CPC-Cerebral Performance Category.

Appendix 2: Summary of Clinical trials for mild hypothermia in TBI.

Author/year	Methods	Results	Conclusion
Clifton et al. [50] .	RCT in 46 severe TBI pts Hypothermia-32 to330 C Study (n=24)Control (n = 23)	Outcome GOS at 3 mo Good recovery C- 36.4/ H-52.2%,	Hypothermia improved neurologic outcome with minimal toxicity
Marion et al. [54].	RCT 82 patients with severe TBI Hypothermia -330C	Outcome GOS-3,,6, 12 mo Outcome at 12mo .H- 62%/ vsC-38% No improvement in pts with GCS 3 /4	Moderate hypothermia for 24 hours in patients with GCSof 5 to 7 hastened neurologic recovery and improved outcome.
Jiang, Yu et al. [52].	RCT- 87pts of sev TBI Hypothermia- 33-350C for 3-14 days, Rewarming-after normal ICP Study- 43 patients. Control- 44 patients	Outcome-GOS at 1yr H- mortality-25.58% good recovery 46.51% C- mortality-45.45% Good outcome-27.27% (p < 0.05) Hypothermia markedly reduced ICP (p < 0.01)	Hypothermia therapy significantly improves outcomes in patients with severe TBI.

Clifton et al. [53].	Multicenter RCT, 392 patients ,Hypothermia- 330 C within 8hr,	Outcomr functional status 6 mo Mortality" H-28%/ N- 27% (P=0.79). H-longer hospital stay due to complications Poor neurological outcome- 57% in both groups	Treatment with hypothermia is not effective in improving outcomes in patients with severe brain injury.
Shiozaki et al. [56].	Multicenter RCT 11 medical centers, 91 severe TBI patients ,ICP could be maintained below 25 mm Hg by conventional therapies (HT group, 45 patients] [NT group, 46 patients)	The incidences of pneumonia, meningitis, leukocytopenia, thrombocytopenia, hypernatremia, hypokalemia, and hyperamylasemia were significantly higher in the HT than in the NT group ($p < 0.05$).	Mild hypothermia therapy conveys no advantage over normothermia.
Gal, Cundrle et al. [58].	RCT sev TBI, HT-15/ NT-15	No difference in the GOS between the HT and NY groups at 6 months (P value 0.0843)	TH not beneficial
Polderman et al. [55].	Prospective clinical trial. 136 sev TBI patients. Hypothermia in pts with no response to barbiturate coma (n=64). Responders control-n=72	Mortality: H-62% vs C- 72%; ($p<0.05$). Good neurological outcome H= 15.7% vs C- 9.7% ($p<0.02$)	Hypothermia improve survival and neurological outcome. Effective in treating refractory intracranial hypertension
Guy L. Clifton et al. [64].	Multi center NABIS:H IIR randomized clinical trial designed to enroll 240 patients	Ongoing	awaited
Jiang [59].	RCT, sev TBI with ICH	TH improves the outcome, significantly decreases intracranial pressure, associated with high incidence of pneumonia and hypokalemia	Not conclusive

Appendix 3: Clinical Trials on Therapeutic Hypothermia for Neonatal Hypoxic Encephalopathy in Term Neonates

Author/year	Methods	Results	Conclusion
Eicher et al. [120].	Systemic cooling to 33 0 for 48hr, HT-32/NT-33 Outcome- rate of death and severe disability at 12mo	Mortality: HT (10/32, 31%)/ NT (14/33, 42%), Sev disability: HT24%/ NT 64%	The combined outcome of death or severe motor scores yielded fewer bad outcomes in the hypothermia group
CoolCap trial Gluckman et al. [75].	Selective head cooling at 33-340C for 72 hrs, HT-116/ NT118, Outcome -Rates of death and severe disability at 18hr	Severe disability or death at 18mo -HT- 59/108 (55%) NT-73/110 (66%) (odds ratio 0.61; 95% CI 0.34-1.09, p=0.1).	induced head cooling is not definitively protective but it could safely improve survival without severe neurodevelopmental disability in infants
NICHD trial Shankaran et al. [121].	Systemic cooling to 33.50 C for 72 hr, HT-102/ NT 106, Outcome -Rates of death and severe and moderate disability at 18mo	Severe disability: HT- [44%] /NT- (62%) (RR, 0.72; 95 % CI 0.54 to 0.95; P=0.01). Mortality: HT-24%/NT-37% [RR 0.68; 95% CI 0.44 to 1.05; P=0.08] cerebral palsy: HT-19%NT-30% (RR 0.68; 95% CI 0.38 to 1.22; P=0.20).	Whole-body hypothermia reduces the risk of death or disability in infants with moderate or severe hypoxic-ischemic encephalopathy.
Lin et al. [122].	Selective cooling to 33-340 C for 72 hr, HT-32/ NT-30, Outcome: Head CT and neurological assessment at 7-10 days	Hypoxic-ischemic changes on head CT HT- 4/30 cases NT-18/28 P<0.01]. NBNA score HT-32+/-2: NT-28+/-3 (P<0.01).	Selective head cooling may be used as a neuroprotective therapy
Robertson et al. [123].	Systemic cooling to 33-340 C for 72 hr, HT-21/ NT-15, Outcome: Mortality, neurological assessment, and eizures	Mortality-HT-7/21/NT-1/15 [More neonates in Sarnat stage 3 in HT [6] where mortality is 100%	Feasible in low resource center
TOBY trial Azzopardi et al. [77].	Systemic cooling to 33-340 C for 72 hr, HT-163/ NT-162, Outcome -Rates of death and severe disability at 18mo	Mortality: HT- 42/NT 44 Neurological Disability: HT- 32 NT- 42 [RR outcome, 0.86; 95% (CI), 0.68 to 1.07; P=0.17]. Infants in the cooled group had an increased rate of survival without neurologic abnormality abd reduced risks of cerebral palsy	TH did not significantly reduce the combined rate of death or severe disability but resulted in improved neurologic outcomes in survivors