ISSN: 2641-1911
DOI: 10.33552/ANN.2023.14.000838
Archives in Neurology & Neuroscience
Iris Publishers

Review Article

Targeted Temperature Management: Systematic Review of Current Literature and Commentary on Future Trends

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Received Date: February 05, 2023

Published Date: February 20, 2023

Abstract

TTM-2 trial results [1] have generated enduring puzzlement regarding the usefulness and goals of targeted temperature management (TTM) in cardiac arrest. The apparent conflict between decades of research and the lessons derived from TTM-2, combined with the unique technical challenges of induced hypothermia, have resulted in a somewhat nihilistic approach to this neuroprotective treatment. The fact remains that temperature manipulation has been used to ameliorate many ailments since the dawn of medicine [2]; In spite of setbacks and uncertainty, TTM continues to be used in cardiac arrest [3-6] and neonatal asphyxia [7]. There is also persistent interest in the potential application of TTM in acute stroke [8], traumatic brain injury (TBI) [9], status epilepticus [10], cardiovascular surgery [11], and other conditions [2]. Strong preclinical evidence shows that hypothermia exerts significant neuroprotective effects, to a degree not attained by comparable therapies [12-14]. In spite of this, translation to the human patient has been disappointing, as the TTM-2 trial results vividly attest. In this review article, we will argue that the discouraging results of some high-profile trials are largely attributable to technological obstacles, rather than a failure of the concept of hypothermia itself. We will also provide an update on current views and applications of hypothermia, discuss the ideal features of advanced thermoregulatory devices and propose technology enhancements to potentiate the impact of future clinical trials.

Keywords: Targeted temperature management; Hypothermia; Neuroprotection; Cooling devices Search methods for study identification

Mechanism of Action

The effects of hypothermia start within minutes [12], shutting down cell metabolism, reducing cerebral blood flow, and restraining cytotoxicity. Each 1°C drop in baseline temperature reduces cerebral oxygen consumption and glucose metabolism by about 5% [15]. Acute brain injuries, such as brain ischemia, trigger parallel cascades of damage that can be attenuated by cooling. Reperfusion injury, for instance, occurs 1-7 days after ischemia and leads to increased oxidative stress and radical oxygen species formation [13]; hypothermia ameliorates the progression of injury by blunting the activation of both intrinsic and extrinsic pathways

of apoptosis. The intrinsic pathway is dislocated early through decreased cJun N-terminal kinase activation, followed by reduction of caspase activation and cytochrome c translocation [16], while the extrinsic pathway is disrupted through inhibition of Fas ligand cleavage [17].

Inflammatory cell migration to injured tissues also contributes to local damage, and neutrophil adhesion to cerebral endothelium is a critical early step in this process. In a rat model of brain ischemia, hypothermia inhibits inflammatory cell recruitment (neutrophils and monocytes) in ischemic tissue by decreasing ICAM-1 expression in micro-vessels, an effect that persisted 1 week post-treatment [18,19]. An in-vitro study showed that mononuclear cells from peripheral blood kept at 33°C produce less TNF-alpha and other proinflammatory cytokines than cells kept at 37 °C after exposure to liposaccharide [20]. Microglial activation can also worsen brain injury [19,21-22]. These cells are activated early after the onset of ischemia, releasing cytotoxic substances like superoxide and nitric oxide, which is inhibited by hypothermia [23].

Preservation of the blood brain barrier is crucial to mitigate injury progression. Hypothermia reduces the impact of ischemia on the cerebrovascular endothelium, by decreasing MMP-2, MMP-9, uPA, and tPA activity, resulting in less hemorrhagic transformation [24]. Hypothermia also curbs microglial nitric oxide generation by inducible nitric oxide synthase [23] and decrease aquaporin-4 expression [25], reducing vascular permeability. The sum of these effects decrease brain edema, which coupled with reductions in cerebral blood volume from decreased metabolic demands, lead to a welcome drop in intracranial pressure (ICP).

The neuroprotective effects of hypothermia persist weeks to months after treatment [12]. Hypothermia promotes cell survival and growth pathways, including Bcl-2 upregulation and promotion of Akt-mediated phosphorylation of proapoptotic proteins [26]. Animal studies show that hypothermia leads to enhanced maturation of neural progenitor cells in the striatum, suggesting that cooling may set the stage for cell regeneration, by preventing stem cell apoptosis through activation of cold-inducible RNA binding protein (CIRP) [27].

Systemic Versus Selective Hypothermia

All cooling devices operate through heat transfer using any of four broad mechanisms: convection, conduction, radiation, and evaporation. Convection occurs when heat transfers from the patient to the environment through air contact, with its rate depending on the speed of air flow. Conduction refers to heat transference from the skin to an object in direct contact with it, which is more efficient than convection (as the rate of heat transfer in water is 32 times greater than air). Evaporative transfer refers to temperature changes associated to shifts in the phase of a substance (for instance, the transition of water from liquid to vapor, as occurs with breathing). Lastly, radiation refers to heat transfer resulting from energy waves generating a temperature gradient between the patient and the environment. This last type of transfer explains most corporeal heat loss at basal metabolic rate. The average person is able to produce heat at a rate of ~1.2 °C/h to compensate for such loss, and shivering can increase this rate to 3.6 °C/h, but at the expense of a 3-fold rise in oxygen consumption [28].

Many cooling strategies are currently used, with a wide range of practicality and efficacy. Invasive or internal cooling methods require percutaneous venous access, with risks of complications, including hemorrhage, thrombosis, and infection (local and/or systemic). A basic example of an internal cooling method is the iv injection of chilled fluids, such as normal saline. This is in fact a frequently used method to rapidly induce hypothermia. An observational study in cardiac arrest patients being transported to a hospital showed that chilled iv saline decreased tympanic temperature by 1.4 ± 0.8°C in ~45 minutes [29]. This treatment, however, has an inherent risk of volume overload and pulmonary edema.

External cooling techniques, on the other hand, have the advantage of not requiring procedures or extensive training of medical personnel. These techniques include surface placement of ice packs, cooling tents, fluid pads, blankets, caps, and helmets. An intermediate degree of invasiveness is achieved by applying liquid coolants in the nasopharynx or esophagus. Trans-nasal evaporative cooling consists in spraying a liquid coolant, perfluorohexane, into the nasal cavity using high-flow oxygen applied through nasal prongs (Rhinochill, BeneChill, Inc., San Diego, CA) [30,31]. All these cooling techniques can be used alone or in combination, in an effort to shorten the time to reach target temperature. For instance, a clinical trial showed that pre-hospital, intra-arrest use of RhinoChill decreased time to reach target temperature after treated subjects were able to receive standard systemic cooling in the hospital [32]. An open label, randomized pilot study, compared 2 techniques to induce cooling in stroke patients, iv saline and trans-nasal evaporative cooling, followed standard systemic cooling [33]; both methods reduced brain temperature by about 1°C within 60 minutes. Although iv saline was faster, its effect started fading 3 minutes after the infusion stopped.

Most existing devices used for neuroprotection induce systemic hypothermia rather than specific head cooling, despite that brain cooling is the goal of treatment. This implies that sedation and airway protection are needed to guarantee tolerance to treatment. As we will see, reducing core body temperature is difficult, and can be associated with dangerous complications. Two devices are mainly used to induce hypothermia in American hospitals: Arctic Sun 5000 (Medivance/Bard, Louisville, CO, USA) [34-36] and Thermogard XP (Zoll, Chelmsford, MA, USA) [37-39]. Artic Sun provides external, non-invasive hypothermia through a kit of four gel-coated pads adhering to the skin, covering a surface area between 0.60 and 0.77 m2 [34]. These pads contain canals where chilled water is pumped through by a controller console. An automatic thermostat controls water temperature within a range of 4 to 42°C, guided by patient's rectal temperature. In essence, this is a refrigerator with a water pump. Contrary to expectation, the pads are not placed strategically over body areas concerned with thermoregulation, such as vascular niches in the ingles, neck, or axillae; instead, they are wrapped around the torso and groins. Another surface device widely used is Blanketrol (Gentherm, Cincinati, OH, USA), a flat quadrangular blanket with an inner water circulating system [34]. Fundamentally, available surface devices

for systemic hypothermia are a recapitulation of the technology developed by Temple Fey between 1938 and 1956, consisting in a zip-up blanket with circulating chilled water through rubber tubes, placed over an insulated mattress [40,41].

Thermogard, in contrast, induces intravascular hypothermia through an indwelling catheter installed in a central vein. Its thermal exchange system consists of endovascular balloons where normal saline circulates in a closed loop system (Figure 1) [39]. The balloons have embedded thermistors that react to temperature changes of 0.1°C, triggering heating or cooling of circulating saline. In general, Thermogard can cool faster and with less core temperature fluctuation during maintenance than Artic Sun [34,35], although some investigators found no meaningful differences between the 2 devices in cooling rates, duration of mechanical ventilation, survival, and neurological outcomes [42,43]. A study comparing several techniques to induce hypothermia found that maintenance of core temperature was out of range almost half of the duration of treatment with Arctic sun and almost all the time with other surface cooling techniques; in contrast, endovascular devices were out of range 3.2 ± 4.8% of the time [34]. A study of ICU nurses found that endovascular devices facilitated visual monitoring and hygiene of treated patients, compared to iced water-soaked towels [44].

Both Artic Sun and Thermogard have significant limitations. Both are expensive, bulky, and can only be used in the ICU (or analogous hospital location) by specifically trained personnel. Both devices can induce metabolic abnormalities, including hypomagnesemia with Thermogard and hyperglycemia with Arctic Sun [43]; the latter is associated with poor neurological outcomes. Systemic infections are common, particularly pneumonia, urinary tract infection and bacteremia [39]. Induction and maintenance of desired temperature are difficult because the actual cooling or heating mechanism is not in direct contact with the patient; such mechanism, built in a unwieldy console, is situated several feet away from the treated subject, resulting in delays in temperature correction or overshooting the target. Systemic hypothermia requires sedation, which is undesirable in patients with acute neurological injuries. Shivering is a common problem, that may require treatment with meperidine, buspirone, dexmedetomidine or other sedatives, and even neuromuscular paralytic agents. Many times air-blowing heating blankets (such as Bair Hugger) are used as adjunct measure to reduce discomfort [45]. Other systemic cooling therapies are implemented using open loop configurations, in which temperature is manually monitored with thermometers, with nursing personnel changing the settings of slow-responding devices. With current methods, the gap between starting therapy and reducing brain temperature by ~3°C (32-34°C) is >30 min and sometimes, several hours. Overall, this approach is inefficient and risks human error.

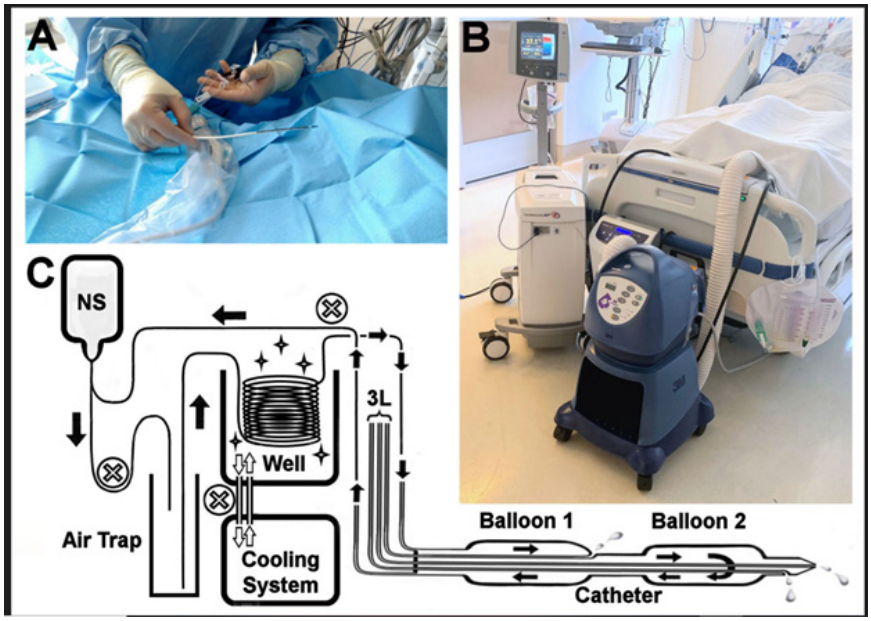

Figure 1: Endovascular cooling device schematics.
Thermogard is an endovascular device frequently used for targeted temperature management. Panel A shows the appearance of its iv temperature management catheter (IVTM). Panel B shows the device's controller console adjacent to a patient's bedside; a Bair Hugger warmer was deployed next to it to reduce patent's discomfort. Panel C demonstrates detailed schematics of the controller console and catheter. Cool or warm normal saline (NS) circulates in a closed loop configuration, passing through an air trap and a cooling well. IVTM catheters have lengths ranging from 22-45 cm and distal flow rates from 1300 to 2100 mL/hour; each catheter has 2 to 5 heat exchange endovascular balloons and a total of 5 lumens: a standard triple lumen (TL) central line and 2 used to circulate the temperature controlled NS to- and from the controller console. Illustration by Lucas Restrepo, MD, PhD.

In contrast, selective (or local) head and neck hypothermia is deemed safer, causing no or negligible reduction in body temperature or life-threatening side effects. Treatment may be associated with local discomfort, increased blood pressure, and bradycardia, all of unclear clinical significance [46]. The capacity of available devices to lower brain temperature, however, is presently unclear. In animal models, both systemic and focal hypothermia decrease infarct volume, albeit focal hypothermia requires a 6-fold longer duration of treatment to achieve similar neuroprotective effects [47]. Similar to systemic hypothermia, delays in tissue cooling can occur during induction. These delays are explained in part by the difficulty in overcoming the heat contributed by blood circulation and intrinsic heat production of the brain [48-50]. Several helmet-like devices have been developed using cold liquids circulating through a canal system [51-54] or cooled gel caps [46,55], all operating through conductive heat transfer from the scalp to the helmet. Harris and colleagues wrote a comprehensive review of existing devices, some of which are briefly described in Table 1 [56]. A small study [51] comparing scalp cooling with 4 devices, showed that all decreased scalp temperatures by 3-6°C within 2.5 to 10 minutes, maintaining low surface temperatures for at least 30 minutes.

Table 1:

Device	Mechanism	Anatomical Area	Advantages	Disadvantages
Ice, icepacks	Passive, connective heat transfer	Head, neck	Cheap Easy to implement	Impractical Difficult to transport Uncomfortable Uncontrolled surface temperature Potential for skin injury Condensation Unreliable
Fanning	Convective heat loss	Head, neck	Cheap Easy to implement	Impractical Ineffective
Foley catheter / high flow oxygen	Convective heat loss by oxygen flow through catheter	Nasopharynx	Cheap Easy to implement	Invasive Uncomfortable Upper airway obstruction Ineffective
Rhino Chill	Convective heat loss by coolant flow through intranasal prongs	Nasopharynx	Easy to implement Portable Mildly effective Can be combined with other techniques	Invasive Uncomfortable Upper airway obstruction Expensive
Frigicap	Passive, connective heat transfer using a precooled gel cap	Skull	Easy to implement Portable Relatively cheap	Needs to be prerefrigerated to −4 °C Cumbersome use (must be replaced every hour to keep cool) Uncontrolled surface temperature Potential for skin injury Scalp pain Increased blood pressure
Blanketrol	Connective transfer using a blanket wrapped around the head and neck	Skull, neck, may cover whole body	May combine selective head/neck cooling and systemic hypothermia	Uncontrolled surface temperature Poor contact to skin Expensive May induce systemic hypothermia
Elkins cap	Connective transfer using chilled fluid circulating through a canal system	Skull, neck	Easy to implement Portable Battery-operated	Uncontrolled surface temperature Poor contact to skin
CoolCap	Connective transfer using chilled water circulating through a canal system	Head	Improves neurological outcomes of neonates with asphyxia	Not portable, bulky, needs electric outlet Tubing system induces water condensation Expensive Complicated to use Needs manual adjustment of radiant warmers Induces systemic hypothermia in neonates Unmonitored surface temperature Interferes with EEG monitoring Scalp and eyelid edema
Sovika Device	Connective heat transfer using precooled gelfilled pads It is	Head and neck	Portable Reusable Adjusts to head and neck	Transportation is problematic (needs storage at 4°C) Uncontrolled surface temperature May induce skin injury
DigniCap	Connective transfer using chilled fluid circulating through a canal system	Head	Adjusts to head and neck Servomechanisms to controls surface temperature Prevents chemoinduced alopecia	Not portable, bulky Expensive Local discomfort

Paxman Device	Connective transfer using chilled fluid circulating through a canal system	Head	Adjusts to head and neck Prevents chemoinduced alopecia	Not portable, bulky Expensive Local discomfort

If cooling is used as a neuroprotective treatment, it should probably target the brain specifically. Naturally, this begs the question whether selective head and neck cooling devices can actually decrease brain temperature. Invasive studies in critically ill patients using catheters with thermistors [57], and non-invasive studies using MRI thermometry show that brain temperature can be reduced by less than 0.5°C after 30 minutes of treatment with selective head coolers [58]. Admittedly, this appears modest and insignificant; however, the technology - not the therapeutic strategy- is in question. Systemic hypothermia is technically challenging and associated with complications that may erase its benefits. Speed of action, ease of use, and practicality, are traits that have largely been neglected in the design of cooling devices. Existing devices are too cumbersome to be transported in ambulances and require electric supplies not available outside of hospitals. Chilled saline, gel caps, and icepacks require refrigerators, which are bulky and prone to water condensation, posing safety risks. There is a need to develop compact, portable devices that can be nimbly carried and easily installed by first responders in the field, to be applied directly to the part of the body that needs the treatment. A selective head and neck cooling device, if safe and effective, would fit the bill.

Clinical Applications of Temperature Manipulation

Cardiac arrest

The principal application of TTM in contemporary medicine is the aftermath of cardiac arrest. Until recently, practice guidelines in the U.S. [3,59] and Europe [4,60] recommended keeping body temperature between 33-36°C for 24 hours after resuscitation. These guidelines were based on randomized [5] and pseudorandomized trials [6] showing improved neurologically-intact survival in hypoxic-ischemic encephalopathy (HIE) patients post cardiac arrest treated with systemic hypothermia (32-34°C for 12-24 hours). This changed after the release of TTM-2 results [1], which showed no difference in mortality or neurological function at 6 months between mild hypothermia and normothermia in 1,850 cardiac arrest patients. As consequence, the latest European Resuscitation Council (ERC) and European Society of Intensive Care Medicine (ESICM) guidelines published in January 2022 did not recommend hypothermia; instead, it suggested preventing fever actively, defined as keeping core body temperature below 37.7 for 72 hours [61]. However, the "certainty of evidence" guiding this recommendation was characterized in their published report as "ranging from moderate to low" [61]. A recent meta-analysis reached similar conclusions [62].

But what was exactly compared in TTM-2? Most enrolled subjects received the same treatment intervention: a cooling device (90% of the hypothermia arm and 40% of the normothermia arm). Of note is that mean temperature at the time of randomization was 35°C, with most patients remaining hypothermic for at least half of the duration of the study protocol. Moreover, outcomes were calculated using an intention-to-treat analysis, which is problematic when one considers that the study intervention, allocating a temperature regulating device, was the same for both groups (with different temperature targets). Perhaps a more informative approach would have been to compare the outcomes of hypothermic individuals (defined as those who had a sustained temperature below 36°C throughout the study period) with those with persistent normothermia. Alternatively, one could ask whether using a cooling device influences outcomes regardless of temperature targets. None of these analyses occurred to the authors, who concluded that there was no difference between groups. Other problems with TTM-2 merit comment. This was essentially a study of European men, which makes the generalizability of results debatable. As in previous studies, different devices (both surface and intravascular) were used as if they were equivalent. This is probably not a valid assumption; as discussed earlier, endovascular devices reach target temperatures faster and maintain it with less variability. Crucially, available data comes from indirect comparisons between different cooling technologies [42].

Controversy about the ideal target temperatures of TTM is hardly new. An earlier randomized, international clinical trial (TTM) compared temperatures goals of 33°C versus 36°C in 950 comatose cardiac arrest patients, showing no significant difference in neurological outcomes [63]. This study was criticized for potential bias, delays to start treatment, quick rewarming, and slow achievement of therapeutic target in the 33°C group (10 hours on average) [64]. TTM-2 directly addressed and improved these sources of error [1].

There is also controversy regarding the effects of hypothermia in patients with non-shockable cardiac rhythms (asystole or pulseless electrical activity). Case-series suggested beneficial effects of hypothermia on both neurologic outcomes and survival among these patients, but other studies showed no benefit or even harm. A meta-analysis suggested better odds of survival and improved neurological outcomes in patients with non-shockable rhythms [65]. In the HYPERION trial [66], moderate hypothermia (33°C) was associated with better neurological outcomes than normothermia (37°C) in cardiac arrest patients with non-shockable rhythms. This trial also demonstrates the inherent technical challenges of induced systemic hypothermia, as target temperature was only achieved after 8 hours on average, and treatment was stopped prematurely in almost 13% of patients. Different cooling methods were used in this trial, including intravascular cooling, closed-loop surface devices, and basic external cooling devices without closed loop (used in 15%, 48% and 37% of cases, respectively).

The duration of TTM is another enduring matter of debate [67]. Animal data suggest improved outcomes with treatments lasting 48 hours [68], but a clinical trial comparing 24 versus 48 hours did not show meaningful difference in outcomes [69]. One of the most

relevant questions in the field is to determine the optimal duration of TTM providing the greatest neuroprotective effects after cardiac arrest. ICECAP (Influence of Cooling duration on Efficacy in Cardiac Arrest Patients) is a NIH-sponsored phase multi-institutional, randomized clinical trial launched in 2020 that will try to answer this question by 2025 [70]. This study has an adaptive allocation design to determine whether increasing durations of induced hypothermia are associated with better rates of good neurological outcomes. A sub-study (PRECICECAP, Precision Care in Cardiac Arrest/ICECAP) will apply machine learning to multimodality data collected from all patients [71]. The motivation for this sophisticated analysis comes from the realization that not all patients respond comparably to the same treatment.

Unsurprisingly, TTM is underused in cardiac arrest: a registry of 45,935 patients with out-of-hospital cardiac arrest in the U.S. between 2013 and 2016 showed that hypothermia was implemented in 46.4% of cases [72]. This is in part due to the burdensome logistics of systemic hypothermia and fear of complications. We would like to argue that such technical barriers leading to underutilization of TTM in the real world fully justify large-scale clinical trials comparing selective cranio-cervical and systemic hypothermia. Another important argument to justify clinical such trials is the fact that hypoxic-ischemic encephalopathy is what usually kills cardiac arrest patients, prompting withdrawal of treatment in the ICU. To date, the use of local hypothermia in cardiac arrest has been limited to the rapid induction or priming in preparation to systemic cooling in the ICU [30,32]. These studies, however, demonstrate feasibility and safety of a more ambitious role of selective cranio-cervical cooling.

Stroke

TTM in stroke patients is both challenging and controversial. Efforts to normalize temperature are widely recommended in stroke patients because fever portends poor neurological outcomes [73], while preclinical studies have shown promising neuroprotective effects of hypothermia in stroke models [13,14,47]. Yet clinical trials in normothermic stroke patients have invariably been disappointing. Table 2 shows a list of ischemic stroke studies and summarizes their characteristics, findings, and shortcomings [74-84]. Part of the problem is that the usual studied intervention is induced systemic hypothermia, which has complications that may offset the neuroprotective effects of treatment. A concern in ischemic stroke is the possibility of a drop in cerebral perfusion pressure to the detriment of ischemic penumbra, given reports of bradycardia and hypotension with cooling, while elevated blood pressure is undesirable in hemorrhagic stroke. Some trials deserve further discussion. The ICTuS-L trial randomized 58 patients with ischemic stroke to 24 hours of hypothermia versus normothermia in addition to standard therapy [76], showing no differences in mortality or 90-day outcomes. A follow up phase 3 trial, ICTuS-2/-3 [78] showed safety of cooled i.v. saline in acute ischemic stroke, but was prematurely stopped because of the success of percutaneous thrombectomy trials (a procedure barred by the study's protocol). More recently, a phase 3 trial, Euro-HYP-1, was stopped after only 98 of planned 1500 patients were recruited, because of sluggish enrolment and termination of funding [81]. Of note is that only 15 (31%) patients randomized to the hypothermia arm achieved the predefined cooling target. The authors' succinct conclusion was: "the feasibility of cooling needs to be improved." This highlights that the principal problem shared by all hypothermia trials is technological. Moreover, the dictum time is brain applies not only to recanalization, but also to opportune implementation of neuroprotective measures. The FAST-MAG trial [85] set a new paradigm: Therapy should be initiated by first responders in the field. Hence, future stroke trials of hypothermia will necessarily resort to portable and easy to operate devices deployable in the field.

Table 2:

Study [Ref]	Study Type	n	Mode of Delivery	Technique Description	Technique Description	Duration Rx	Mean time to TT	Limitations	Complications
Schwab et al [75]	Uncontrolled descriptive feasibility study	25	Systemic hypothermia	Surface cooling with cooling blanket with a ventilator air fanning †	33°C	48-72 h	3.5-6.2 h	- Critically ill patients - Sedation needed with fentanyl and Propofol - Neuromuscular blockade atracurium infusion - All patients had large MCA stroke. - Therapy implemented 14 h after onset of symptoms	- Pneumonia in 40% of patient - Thrombocytopenia - Elevated amylase/lipas - Arrhythmias, prolonged PR and QT

Cleveland Clinic Study [82]	Uncontrolled descriptive feasibility study	18	Systemic hypothermia	Combination of techniques including cooling blanket ‡	32°C	12-72 h	3.2±1.5 h	- Small study - Labor intensive - Critically ill patients - Early neuromuscular paralysis with atracuronium - Sedation with propofol	- Overshoot temperature in 78% patients - BradycardiaHypotension - MI
ICTuS [78]	Uncontrolled, multicenter, development, feasibility	18	Systemic hypothermia	Endovascular device using Celsius Control system *	33°C	12-24 h, rewarm 12 h	.	- Meperidine and buspirone needed for shivering	- Shivering
ICTuS-L [76]	Randomized controlled	58	Systemic hypothermia	Endovascular device using Celsius Control system * in awake patients	33°C	24 h, followed by 12 h rewarming	138.3±198.9 min	- Invasive - Requires trained personnel in ICU - Sedation needed for shivering - Target temperature not reached in 8 patients (28.6%) - Device console failure in 2 patients - Shivering led to increased target temperature (34°C). Patients received IV fibrinolysis	- Pneumonia - DVT - Oliguri - Sedation
ICTuS 2/3 [77]	Multicenter, prospective, randomized, Phase 3 trial	120	Systemic	IV saline followed by endovascular device *	33°C	24 h followed by 12 h rewarming	2 H	- Concomitant use of IV fibrinolysis - Invasive device - Treatment started 287.6±65.8 min (range, 175–477 min) after onset of symptoms - Study suspended prematurely	- Pneumonia in 29% treated cases
Euro-HYP-1 [81]	Multicenter, prospective, randomized, controlled Phase 3 trial	98	Systemic	Either surface (77% cases) or endovascular	34-35°C	24 h	Published graph shows mean temperature never reached 35°C during initial 10 h	- Study prematurely stopped - Most patients (69%) did not achieve target temperature - Different cooling methods used, complicating analysis	38% of hypothermia pts had an adverse event, mostly pneumonia and systemic infections
iCOOL1 [33]	Prospective, interventional, open label, two armed, single center trial	20	Combined regional and systemic	IV saline versus transnasal evaporative cooling	N/A	60 min	Lowering of -1.5°C of head/core within 1 h	- Small sample size - No control group without cooling - Both ischemic and hemorrhagic stroke enrolled - Patients were intubated in neuroICU	- Shivering and elevated BP with iv saline - Epi-pharyngeal bleeding, edema nasal conchae with RhinoChill

Helsinki University Central Hospital Study [84]	Single-center randomized controlled open safety and feasibility trial	36	Systemic hypothermia	Surface cooling device (Criticool), induction with cold saline iv, and cooling blankets wrapped around the patient's chest, waist, and limbs	34.5° C	12 h	4.5 h	- Small sample - Single center - Requirement of meperidine, dexmedetomidine and buspirone - 15/18 (83%) patients assigned to hypothermia reached primary outcome measure, keep <36°C body temperature for >80% of the 12 h cooling period.	- Shivering - Bradycardia - Elevated BP - Pneumonia in 39% of cases
ReCCLAIM I [79]	Single-center, prospective single-arm open-label clinical trial	20	Systemic hypothermia	Endovascular device (Thermogard)	33°C	12 h	64±50 min	- Severe stroke cases - Patients were critically ill - All patients undergoing endovascular embolectomy - Requirement of meperidine, demedetomidine and buspirone Invasive, super-selective IA injection, requires specialized setting	- Shivering - Bradycardia - Elevated BP - Pneumonia in 25% of cases
Korean study 2 Center Study [83]	Two-center, prospective two-arm openlabel clinical trial	75	Systemic hypothermia	Endovascular device (95% patients) or surface device **	34.5° C	48 h	378±355 minutes	- All patients were mechanically ventilated - Sedation with midazolam and neuromuscular paralysis with vecuronium - All patients had recanalization (spontaneous or endovascular) - Rewarming over a 48 h period	- Bradycardia - Elevated CK - MI

Notes:

†Polar Bair (Bair Hugger Temperature Management Systems), Augustine Medical, Eden Prairie, MN

‡Aquamatic K-Thermia EC600, American Medical Services, Bellville, OH

*Innercool Therapies was acquired by Philips on July 15, 2009; Philips Healthcare, Best, The Netherlands

**Alsius Corporation was purchased on May 5, 2009 by Zoll Medical Corporation

Traumatic Brain Injury and Increased Intracranial Pressure

More than 50 million people each year suffer TBI, and roughly half of the world's population is expected to sustain at least one TBI episode in their lifetime [86]. TBI has a spectrum of severity and many mechanisms of injury, which is problematic in clinical trials because enrolled patients may not be comparable. Most TBI cases are classified as "mild" (i.e., concussions); however, the deleterious effects of apparently trivial trauma have become obvious, particularly if repetitive, increasing the risk of chronic cognitive difficulties, PTSD, depression, substance abuse, and suicide [87,88]. Military personnel have a high TBI risk, not only during battle, but also during training and transportation [88]. Importantly, concussions do not have specific treatment; hypothermia has been reserved for severe injuries.

Hypothermia trials for severe TBI have had conflicting or disappointing results. A possible explanation is that used technology was ineffective at cooling the brain in a prompt, sustained, and safe fashion. The limitations of available cooling technologies were patent in the POLAR trial [89], which compared normothermia with cooling using iv chilled normal saline administered in the field, followed by surface cooling upon hospital arrival. This trial, involving 511 TBI patients, showed no difference in neurological outcomes between the active treatment and control groups. Of note is that goal temperature reduction to 33°C was never achieved in 27% of treated patients, while the remaining subjects reached the temperature goal 10 hours after the time of injury (range: 6.8 to 15.9 hours). Hence, these results ostensibly point to unresolved technological shortcomings, rather than failure of hypothermia as TBI treatment.

The potential role of hypothermia in TBI has been studied in many prior clinical trials [90]. The first RCT [91] compared moderate hypothermia for 24 hours to normothermia, in 82 patients with severe closed TBI, showing that the active treatment arm had faster neurological recovery and better clinical outcomes. A more recent prospective multi-institutional trial [92] enrolled 392 subjects with coma secondary to closed TBI randomly assigned to normothermia or cooling to 33°C within 6 hours of injury; the hypothermia group had more hospital days with complications

than the normothermia group, although their ICP was lower. The major drawback of this study was the rudimentary technology used to induce hypothermia, and the fact that the authors did not report how successfully target temperature was maintained.

In spite of these caveats, hypothermia can reliably decrease ICP, which is an important cause of secondary injury and mortality associated with TBI. The Eurotherm3235 Trial evaluated the role of hypothermia in ICP reduction after TBI [93]. The study randomized subjects with ICP >20 mmHg to standard care versus hypothermia (32 to 35°C) plus standard care, showing that the latter was more effective at decreasing ICP. In spite of this, the hypothermia group had worse outcomes. A drawback of the study was its early termination due to safety concerns, which may alter external results validity. Additionally, there was no blinding to the intervention, which could lead to an increase in reported adverse events. To sum up, two deficiencies quickly emerge after reviewing the TBI literature: reliance in systemic hypothermia, and absorbed interest in severe TBI, ignoring milder cases, including concussions.

Temperature Regulation in the Operating Room

Perioperative normothermia is associated with improved surgical outcomes [94]. The current standard is to monitor temperature during anesthesia and keep normothermia, unless there is a specific exception. Thermoregulation is compromised by surgery, due to anesthesia (regional and general) and core exposure during invasive procedures. Hypothermia is common in hospital's infamously cold operating rooms. Hyperthermia is less common, but can occur as consequence of certain pharmacological interventions, which is more ominous and has to be identified immediately. Medications given post-operatively, opioids in particular, can impair thermoregulatory recovery. As result, normothermia may be delayed for 2-5 hours, depending on the magnitude of intraoperative hypothermia and patient's age [95]. Mild hypothermia in the perioperative period is associated with complications such as impaired drug metabolism, prolonged recovery from anesthesia, cardiac arrhythmias, coagulopathy, wound infections, and shivering. There are different strategies to reach and maintain normothermia. Prewarming reduces body thermal redistribution and hence, can help attain intraoperative normothermia. Forced warm air blankets [45] and circulating water garments are effective.

Fever Treatment and Prevention

Fever is one of the most frequent applications of cooling. It is also deleterious to acute neurological injuries: each 1°C increase in body temperature doubles the relative risk of poor neurological outcomes in ischemic stroke [73]. Some neurological injuries, such as subarachnoid hemorrhage and hemispheric infarction, are almost always associated with a severe systemic inflammatory response that includes fever. Therefore, maintaining normal temperature is justified. A study showed that endovascular devices essentially suppressed fever in a cohort of patients with severe stroke, compared to an escalating protocol including surface methods and pharmacological antipyretics (1.5±3.3 versus 9.3±14.5 hours of fever burden) [39].

Neonatal Asphyxia

Cooling improves the outcomes of HIE due to neonatal asphyxia [96-101]. Guidelines recommend inducing hypothermia 6 hours post-partum, maintaining core temperatures of 33.5-34.5°C for 72 hours, and re-warming at 0.5°C per hour [102-104]. Computed data from 11 randomized controlled trials shows that hypothermia significantly reduced the combined risk of death and major neurodevelopmental disability (RR 0.75, 95% CI 0.68 to 0.83) [105]. One needs to treat 11 babies to save the life of one, or treat 8 patients to prevent neurodevelopmental disability in one child [105]. The beneficial effects of treatment are observable at 18-24 months and at 6-7 years of age [106]. Hypothermia can also prevent seizures [107,108] and cerebral palsy in HIE patients [109]. In spite of these meaningful figures, hypothermia is underused. One reason is that most hospitals lack the capacity to deliver this treatment. Almost all newborns with HIE need to be transported to a tertiary referral center [110], sometimes located hours away, causing delays which may impact outcomes. Many patients do not receive treatment during transportation, while some receive unmonitored cooling with surface methods or passive hypothermia (removing external heating). Not surprisingly, more than half of patients do not achieve target temperature upon arrival to the tertiary care center [111]. Part of the problem is that newborns are challenging patients, as they simultaneously depend on brown fat stores and shivering for thermo-regulation [104]. Many treated patients reset their core temperature, complicating warming. As result, it is difficult to keep their temperature steady.

In practice, neonatal hypothermia is usually induced with either body surface cooling devices or selective head cooling. Both methods induce systemic cooling, and their clinical effectiveness is deemed equivalent [102-104, 112]. Blanketrol (Cincinnati Sub-Zero, Cincinnati, OH) [96] and Cool-Cap (Olympic Medical, Seattle, WA) [97] are widely used surface cooling devices. The first consists of a blanket placed under the neonate's body; this device is bulky, needs an electric outlet connection, and its tubing system induces water condensation. Cool-Cap has the same shortcomings of Blanketrol, but it is more expensive and complicated to use, requiring manual adjustment of radiant warmers [113]. Cool-Cap also interferes with EEG monitoring and is associated with scalp and eyelid edema. Both devices are reiterations of the same familiar concept: connective heat transfer from patients to an external tubing system with circulating refrigerated water. Water is not a good heat conductor, given its high specific heat capacity. Much time and energy are needed to change water temperature, creating a time lag from the moment settings are changed to the achievement of goal temperature. The result is that these devices tend to overshoot target temperatures. Because of servo-control mechanisms, Blanketrol provides more stable temperature. Overshooting core temperatures to ≤30°C may induce coagulopathy in patients who already prone to intraventricular and systemic bleeding. Both devices can also expose patient's head to surface temperatures >38°C during temperature adjustment and rewarming, as the main system feedback is core body temperature. As with most technologies used in adults, lack portability is a major problem in neonatal cooling devices, which is of outmost relevance

during intra- or inter-facility transportation [112,114].

Prevention of Chemotherapy-Induced Alopecia

Chemotherapy can cause alopecia, which is cited among the most distressing aspects of cancer treatment. Selective scalp cooling reduces circulation to hair follicles and inhibits local metabolism, preventing tissue exposure to chemotherapeutic agents. Research shows that 38.5W of heat must be extracted from the scalp to cool hair follicles to 22°C [115]. Two scalp cooling devices have been evaluated in clinical trials to prevent alopecia in women with early stage breast cancer: DigniCap (Dignitana AB, Lund, Sweden) [116] and Paxman Scalp Cooler (Paxman Coolers, Ltd. Huddersfield, UK) [117]. DigniCap prevented hair loss in 70% of patients with breast cancer receiving neo/adjuvant chemotherapy, while all untreated controls experienced hair loss. This device consists of a silicone cap adjusted to the head, cooled with circulating monopropylene glycol. The coolant is pumped by a control unit, keeping scalp temperature above freezing (usually around 15°C) using automatic servomechanisms. The Paxman cap operates similarly. In a randomized trial comparing the Paxman cap and no treatment, the former resulted in hair loss reduction of ~50% [118]. A major concern about scalp cooling is the possibility of shielding cancer metastasis in treated skin from the effects of chemotherapy, with negative impact on survival. After a median follow-up of 2.5 years, none of the patients treated with DigniCap developed scalp metastases. A study showed similar mortality rates in non-metastatic breast cancer among scalp-cooled women and controls who did not receive cooling [119]. In spite of FDA approval, both devices are not widely used because they are not typically payed by health insurance. Treatment alternatives are technologically crude. They include Penguin caps, which use dried ice, and pre-cooled gel caps. Both require multiple changes every 30 minutes, and scalp temperature is uncontrolled. Unmonitored surface temperature is a liability, with clear risks of frost bite. These techniques require considerable refrigerated storage space, crowding infusion centers.

Other Applications

Cooling is both analgesic and anesthetic. In the midst of the opioid epidemic, there is a need for non-pharmacological therapies to promote recovery from acute pain syndromes and surgery, sparing the use of medications with potentially serious side effects, including addiction. Although cooling is frequently used by migraineurs and patients with back pain, therapy is deemed impractical and tedious, usually delivered through icepacks changed every 10-20 minutes. Alternating application of hot and cold to the skin surface is used to mitigate muscle injury after strenuous exercise on performance athletes [120]. This is usually done with ice or cold packs, followed by heat pads. Contrast therapy is thought to speed recovery by removing injured tissue metabolites such as lactic acid, reducing post-exercise edema, and enhancing local blood flow [120,121]. Data from 18 randomized-controlled trials of cold water therapy (including cold water immersion) following exercise [120], found that treatment significantly improved pain compared to passive recovery, although studies were deemed of limited quality and risk of bias. Research is needed to determine optimal hot to cold time ratios, best modality of contrast delivery, and total duration of treatment. No devices are capable of delivering contrast therapy. Game Boy GRPRO (CoolSystems, Inc., Concord, CA) is a widely used device for athletes, which uses circulating water chilled with ice. It is portable, but bulky and cumbersome to use, as ice has to be constantly replaced. A new version, Game Ready Med4 uses refrigerated water, but is not portable. Local heat or contrast therapy is often recommended as adjunct treatment of back pain, but is limited by impractical heat delivery means, including warm compresses and heating pads.

Hypothermia may also help control seizures [10]; since age of Hippocrates, physicians have observed a deleterious relationship between hyperthermia and epilepsy [122]. Interestingly, synaptic transmission is attenuated by cooling [122-123]. Thermoelectric coolers have been used to cool epileptogenic areas of the brain [122,123], a technology limited by ineffective means to dissipate heat extracted from target tissue.

Conclusions

Hypothermia is a versatile treatment, used in problems as diverse as cardiac arrest and chemotherapy-induced alopecia. Regardless of its application, cooling has a number of practical and technological barriers, including portability, ease of operation, speed of target temperature induction and stability. Most current technologies are based on refrigeration units capable of pumping chilled water through pads in contact with the skin or indwelling catheters. Future technologies will likely resort to electronically controlled elements applied to the skin. Finally, an important question to be resolved is whether neuroprotection can be achieved with head and neck cooling, rather than systemic hypothermia.

Acknowledgement

None.

Potential Conflicts of Interest

Dr Velez has no conflicts of interest; Dr Julio Vergara is co-founder, co-owner and Chief Science Officer of Hypothermia Devices, Inc. (dba Kelvi); Dr Lucas Restrepo is co-founder and co-owner of Hypothermia Devices, Inc. (dba Kelvi)

Search Methods for Study Identification

Our search strategy included inquiries of MEDLINE, the Cochrane Central Register of Controlled Trials, previous reviews, cross-references, abstracts, conferences, symposia proceedings, expert informants, and journal handsearching. We limited searches to publications in English.

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