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REVIEW ARTICLE

Hypothermia as a Neuroprotectant for Neurorehabilitation Eligible Patients: State of the Art Review and Update

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ABSTRACT

Applying therapeutic hypothermia (TH) for the purposes of neuroprotection, originally termed "hibernation," started nearly 100 years ago. As advances in the medical and surgical management of patients with neurotrauma has increased survivability and minimized primary damage, significant research has been directed at identifying neuroprotective mechanisms that might mitigate the secondary damage which leads to neurological worsening and impedes recovery. As therapeutic hypothermia cooling systems have improved to the point where it is practical and safe for general application, interest in providing such treatment in conditions such as spinal cord injury, traumatic brain injury, stroke, and cardiac arrest has increased. This manuscript will review the mechanisms by which therapeutic hypothermia mitigates secondary neurological injury, the clinical scenarios where therapeutic hypothermia is being applied via Spinal Cord Injury (SCI), Traumatic Brain Injury (TBI), and Stroke (CVA), and review published studies utilizing therapeutic hypothermia for central nervous system neuroprotection in translational studies.

Keywords: Spinal Cord Injury, Hypothermia, Neuroprotection, ASIA score, Trauma, Methylprednisolone, Stroke, Traumatic Brain Injury, TBI

Introduction- History of Hypothermia as a Neuroprotectant

As knowledge regarding neurotrauma revealed the complex pathophysiology of "secondary neural injury cascades," interest in preventing such secondary damage using hypothermia (and preventing hyperthermia) re-emerged. Neuroprotection via applying hypothermia, originally termed "hibernation," started nearly 100 years ago. Initially, the treatment was used in patients with intracranial abscess and high fevers which could leading to severe brain injury[1]. More recently, sophisticated cooling systems using thermocouples and feedback sensors have enabled precise and sustained core temperature regulation. Thus, the safety of hypothermia improved so that that it is practical and widely applied. These advances fueled further interest in hypothermia research, as neuroprotection protocols have been developed for multiple central nervous system pathologies, including traumatic brain injury (TBI) and spinal cord injury (SCI). Finally, multiple studies have been published to support hypothermia as safe and effective to improve the long-term outcome of these neurological catastrophes (foot note). This paper will serve to review such studies and mention the most recent.

Historical publications on the use of therapeutic hypothermia (TH) in clinical neuroprotection began in 1943 with a case of traumatic brain injury. The process was termed "generalized refrigeration[2]". In 1951 and 1956, two additional case reports utilizing TH – "hibernation" on patients with brain abscesses were published[3]. Later studies focused on development of animal models and the idea that TH could reduce secondary damage after brain trauma by reducing cerebral ischemia[4]. A study published in 1996 revealed seven of 10 patients given moderate hypothermia (core temperature 32.5°C–33.0°C for 24 hrs.) with severe closed head injury (Glasgow Coma Scale score < 7) made a "good" recovery[5]. The effects seen were reductions in intracranial hypertension, cerebral oxygen consumption, and cerebral ischemia. Another study found the cooling group (n=46) subjected to TH had reduced seizures and more patients recovering to a good recovery/moderate disability level vs. remaining at a severe disability/vegetative/dead level[6]. However, concerns were also raised in these studies regarding potential hazards of the TH treatment as although reversible with re-warming, increased levels of lipase and pancreatitis were seen. While a statistically significant increase in the PTT and PT, just out of the normal range, was found during and after re- warming, there were no clinically significant problems with bleeding[6].

Core temperature regulation and hypothermia.

Therapeutic hypothermia is defined simply as the reduction of mean body core temperature to create some medical benefit[7]. As warm-blooded mammals, humans regulate their core body temperature within a constant and narrow range and will not tolerate even short periods of hypothermia without engaging compensatory mechanisms. Hypothermia induces a variety of human responses to combat hypothermia. These thermoregulatory mechanisms in humans have two components: behavioral and hypothalamic[7]. External behavioral mechanisms to increase core temperature could include clothing, shelter, warm baths, or seeking environments with higher external temperature. In the ICU setting, patients often have no or limited control over these mechanisms.

Arteriovenous shunting, inducted vasoconstriction, and shivering are all internal mechanisms of reducing hypothermia. In any type of TH treatment, these compensatory mechanisms need to be curtailed, monitored, or modified. The site of internal thermoregulation is most likely the hypothalamus[8]. Involuntary shivering creates muscle activity that increases metabolic heat production as the temperature drops below 36.5C. Shivering is initiated by regional vasoconstriction and becomes severe at core temperatures under 35.5C. Non-shivering thermogenesis does occur in adults to combat hypothermia but plays a minor role compared to shivering[9]. Shivering is a highly effective mechanism that increases metabolic heat production many times over, thus effectively raising core body temperature.

Mechanism of neuroprotection in hypothermia

METABOLIC RATE OF OXYGEN CONSUMED

Reduction in the metabolic rate of oxygen consumed by the brain and spinal cord is the primary neuroprotective effect of hypothermia applied as therapy in acute neurotrauma[10]. By reducing the metabolic rate of oxygen consumption, the energy rate utilized might be reduced and glucose utilization might be improved. One measure of brain oxygen consumption places the magnitude of the reduction at 5% for each degree Celsius the body temperature is reduced[10].

Often, neurotrauma causes a hypermetabolic state as the damaged neuronal tissue deals with repair. As inflammatory mediators and free radicals are "cleaned up," lactate accumulates and alters PH creating an acidotic state. Applied hypothermia, by slowing metabolism, has been thought to reduce interstitial lactate accumulation. For every degree

(Celsius) that body temperature decrease, the PH increases by 0.016[11] supporting the theory that TH protects from neurological injury by reducing acidosis. Despite the "neatness" of this theory, other investigators have questioned the actual measurements and theory altogether[4].

Clinical Application

PATIENT EVALUATION OVERVIEW

Patients felt to be candidates for TH include all patients with conditions exacerbated by secondary injury to the central nervous system. The mechanisms of such secondary injury include Wallerian degeneration, vascular ischemia, formation of cytotoxic edema hyperinflammatory response, ionic alterations, accumulation of neurotransmitters in a pathologic fashion, release of arachidonic acid, production of free radicals, and failure of ATP dependent processes. The protective effects of hypothermia involve suppression of the injury-induced immune response detailed above and thus, over-inflammation[12].[13]. The protective effect also occurs by reducing vasogenic edema, inhibiting polymorphonuclear chemotaxis[14] and reducing gliosis[15]. Hypothermia also reduces glutamate-mediated neurotoxicity and further oxygen free radical production[16]. Such processes are seen classically in traumatic brain and SCI, where prevention of secondary neuronal damage through TH has been of great interest. Similarly, patients who have post-acute ischemic stroke (CVA) and hemorrhagic stroke (ICH) also fit the profile of those who could potentially benefit from TH[17]. Later we will present specific outcome studies, recent and remote, establishing the efficacy.

In the setting of neurotrauma, when a new intervention is proposed, complete neurological recovery is typically the main aspiration. However, we would argue, with even small or incremental gains, patients can often see tremendous functional improvements and quality of life gains. Therefore, interventions that allow even small incremental neurological improvements can be extremely helpful and satisfying. For example, in stroke patients a smaller "penumbra" can make the difference between ambulatory and non-ambulatory status. For cervical SCI patients, incremental recovery of just one spinal level can translate into meaningful gains in the ability to perform self- care (Activities of Daily Living (ADL) and functional tasks. For example, improving from a C6 SCI level to a C7 injury level can translate into the ability to propel a manual wheelchair or manipulate a urinary catheter. Improvement to a C8 level increases hand function to the point that an assistive device may not be needed with upper limb ADL activities such as eating or dressing.

The setting of CNS ischemia is an even more promising area for TH. In comatose survivors of cardiac arrest two high quality studies showed that therapeutic hypothermia not only significantly improved survival but also improved the neurologic outcome after different courses of cooling treatment[18]. Compared to historical controls without hypothermia, 56% of patients showed favorable neurological outcome vs. 26% in the normothermia control group[19].

Another group where TH is being explored is in those with aneurysmal subarachnoid hemorrhage (SAH)[20]. Therapeutic hypothermia has been utilized to treat the development of delayed cerebral ischemia which can lead to cerebral infarction associated with poor outcomes. The focus of hypothermia treatment has been to reduce cerebral vasospasm (CVS), a delayed morphological narrowing of cerebral arteries, occurring 4 to 10 days after SAH. TH has also been considered for patients with SAH during aneurysm surgery[21] or patient who present immediately after rupture.

COOLING METHODOLOGIES

The development of closed-circuit intravascular cooling catheters has greatly enhanced the safety and efficacy of hypothermia delivery. External cooling through transcutaneous pads or suits can provide a non-invasive method for reducing body temperature, but precise control remains elusive and surface heat exchange devices can interfere with sensory neurologic testing[22].

Two brands of FDA approved catheters have become commercially available utilizing closed-circuit feedback mechanisms to regulate heat exchange[23]. These devices increase the rate at which core body temperature can be reduced and effectively regulate the temperature within a narrow therapeutic window[24]. Because skin sensation contributes disproportionately to the perception and discomfort of cooling, endovascular cooling is also far more comfortable for awake patients than surface cooling. Skin counter-warming can also be used together with endovascular cooling to lower the shiver threshold and improve comfort without adversely affecting the core temperature[25].

Bradycardia is a predictable consequence of cooling, with a mean decrease in 10- 12 beats per minute when comparing baseline to target temperature[26]. Intravenous adrenergic agents, which are frequently used to treat hypotension from neurogenic shock, can be helpful for treating induced bradycardia[26] Intravenous pacing for

excessive rate depression in refractory cases can be used temporarily as well if necessary.

Shivering associated with systemic cooling creates patient discomfort, increases metabolic demands, and can lead to difficulties in reaching target body temperature. For patients not on mechanical ventilation the management of shivering can typically be accomplished with the use of pharmacologic agents. In a review by Kranke, meperidine, 25mg was found to be an effective agent for control of acute symptoms[27]. Control of shivering will be at the discretion of the treating center, and because of its adverse effects on patient comfort and effects on body temperature, should be pharmacologically treated. Shivering is more common following thoracic level injuries and is less commonly encountered with cervical SCI patients.

Hypothermia in the spinal cord injury population

HISTORICAL PERSPECTIVE

therapeutic hypothermia has been applied in the setting of SCI for the past seven decades[28]. The lack of proven neuroprotectants for acute SCI underscored the urgency and importance of exploring alternative interventions. The idea of utilizing TH in the area of SCI cord injury was brought forth in the 1950's in a dog model and in 1968 in a study on primates[29] [30]. Localized spinal cord cooling with a simple liquid perfusion unit produced effective selective reduction of spinal cord temperature. "Thirteen monkeys who had complete lower extremity paraplegia following induced impact injury at T10 followed by incision of the dura 4 hours later and localized spinal cord cooling for 3 more hours showed an excellent return of neurological function"[31]. Studies like this led to initially increased interest in local vs systemic cooling the spinal cord in humans. In addition, local application of cooling in SCI was possible for short periods of time because the injured segment of the spinal cord is exposed for a short period of time as most patients with traumatic SCI had to undergo surgery.

Despite this early interest, enthusiasm for therapeutic for treatment of SCI waned in the 1970's and 1980's due findings published that suggested new pharmacological agents were effective for neuroprotection. These initial studies results created great excitement in the use of high dose methylprednisolone, which for a period became standard care for acute SCI[32] [33] [34] [35]. Other anti-inflammatory infusion agents such as nalaxone and tirilazad mesylate also showed initial neuroprotective promise. In the mid 1990's, doubt emerged regarding the use of methylprednisolone[36] and the other agents proved ineffective. Further analysis of the original published research suggested a higher rate of complications and the amount of neurological recovery was felt to be minimal[37], and ultimately high dose methylprednisolone for SCI was abandoned in many specialized canters and research focus returned to hypothermia.

The feasibility and utility of using hypothermia reached widespread public awareness with the use of hypothermia in the management of a high visibility NFL game when Kevin Everett [38] was treated with TH and made dramatic functional gains in the following months. Many Americans, for the first time, witnessed the patient's injury and then saw him walk across the stage at an awards show months later. After such a perceived threshold of benefit and safety had been reached, further advances focused on refining the time and duration of cooling and the importance of the pace of rewarming.

Although many focus on complete cure, in this patient population incremental improvements in long-term neurological function of even just one level can have a significant health-related and socioeconomic impact.

ANIMAL SPINAL CORD INJURY STUDIES

In 1992, Martinez-Arizala and Green at the University of Miami reported that pre- and post-treatment with moderate hypothermia (31-32°C) was effective in decreasing the degree of hemorrhage at the site of primary injury in rats[39]. This study provided evidence that an early cooling strategy was the desired approach vs later cooling. The idea was by lessening the deleterious effects of trauma on the spinal cord microvasculature one could reduce local swelling. The study also confirmed that more aggressive cooling was not necessary to realize hypothermia's neuroprotective effects.

Follow-up studies at the University of Miami Miller School of Medicine by Dietrich and colleagues demonstrated that systemic hypothermia resulted in concomitant epidural cooling that was neuroprotective for contusive injuries in rat studies[40]. Open field locomotor testing demonstrated that rats exposed to hypothermia exhibited improved scores as early as one week following injury. Furthermore, this trend continued throughout the study and became more significant by the end of the 44 days studied [40].

Histologic analysis of the contused spinal cord at 7- and 44-days post-injury demonstrated hemorrhagic necrosis, cell loss, axonal swelling, and vacuolization

typically seen following SCI. However, in the hypothermia-treated group sparing of grey and white matter was seen with smaller associated contusion volumes and reduced rostral-caudal spread. Histology demonstrated a mean 15.8% reduction in lesion size in the hypothermia-treated animals[41].

These findings in a thoracic model of rodent SCI have been confirmed using a recently developed rat model for C5 cervical spinal cord injury as described by Pearse, et al.Rats randomized to receive moderate hypothermia at 33° C delivered externally for two hours after injury were found to have improved neurological outcomes in forelimb function [42]. This study confirmed work done back in 1979 where measures of forelimb gripping force were reduced significantly in the normothermic animals versus the animals where hypothermia was applied($p<0.05$)[43]. The weight-supported forelimb hanging test showed significantly improved ability as well from 3.3 $\pm$ 1.1 seconds to 5.8 $\pm$ 1.0 seconds ($p<0.01$) [43].

More recent studies included Hosier et al., who found that hypothermia improves motor function seven days after a traumatic spinal cord injury compared with controls in female rats[44]. Xu et al. in 2016 found that rats treated with local epidural saline infusion hypothermia achieved significantly higher BBB scores than control up to 3 weeks after injury[45]. Finally, in 2019, Jorge et al. found that inducing hypothermia via systemic surface cooling in rats with thoracic spinal cord injury had significantly higher BBB scores 6 weeks after injury[46]. Finally, according to a 2022 systematic review evaluating neurological recovery and postoperative complications after therapeutic hypothermia found that among the 24 preclinical animal studies, both systemic and local hypothermia significantly improved neurologic recovery, including improvements in urinary function[47].

CLINICAL EVIDENCE OF EFFICACY - EVALUATION OF OUTCOMES

Levi published in 2009, a pilot clinical study to assess the safety and effects of moderate intravascular hypothermia (33.0 $\pm$ 0.5° C) in the setting of acute traumatic cervical spinal cord injury[48]. Patients were cooled intravascularly with a target temperature of 33.0 °C per hour at a maximum rate of 0.5° C per hour, with maintenance of hypothermia for 48 hours using the Alsius CoolGard® Icy Catheter (Zoll Medical, Chelmsford, Massachusetts), an FDA approved (510k #K030421) cooling catheter placed into the femoral vein. This was followed by slow re-warming at 0.1° C per hour to prevent rebound hyperthermia. Catheter placement occurred in the Emergency Department and patients were managed in the intensive care unit while hypothermic. "There was no contraindication to early surgery, traction, or imaging. Blood pressure support was utilized as needed to maintain a mean arterial pressure of > 90 mm Hg. A second confirmatory neurological exam was performed 12 hours after injury with no sedation. Over a period of 25 months 14 eligible patients were enrolled into the treatment. None of the patients received the high dose solumedrol protocol."[48]

The distribution of injuries included C4 (21.4%), C5 (50%), and C6 (28.6%). There were no instances of neurological worsening, and at median 1 year follow-up 6 of 14 patients (42.8%) converted from complete to incomplete SCI. "Three (21.4%) regained sensory function, converting to AISA B, and three regained motor function converting to AISA C (14.3%) or D (7.1%)"[48]. All recoveries occurred when transferred to inpatient acute neurorehabilitation.

Dididze et al, published findings on 35 complete ISNCSCI A SCI patients undergoing modest cooling (33 degrees). Four converted to ISNCSCI B in <24 h post injury. Fifteen of total 35 patients (43%) improved at least one ISNCSCI grade at latest follow up 10.07 ($\pm$1.03) months. Both retrospective (n=14) and prospective (n=21) groups revealed a similar number of respiratory complications[49]. Currently the University of Miami Miller School of Medicine is conducting a multicenter trial on patients undergoing hypothermia immediately after acute SCI with multiple outcome measures.

In looking back at what has also been published, a meta-analysis done on 2022 by Shin et al, on the effect of hypothermia in acute spinal cord injury (SCI) found that more than half of patients experience neurological improvement after hypothermia. The meta- analysis included eight retrospective studies with a total of 103 patients who were provided hypothermia treatment for SCI. Interestingly, of the patient pools studied, the proportion of patients who improved after systemic hypothermia was 70.9% as opposed to 52.5% in those who had local hypothermia. This outcome is attributed to lower levels of apoptosis and anti-inflammatory effects, though there may also be more associated complications[50]. Overall, it seems that protocols calling for mild hypothermia for shorter durations and severe hypothermia for prolonged periods have not shown favorable outcomes[51]. Rather, the goal is a "Goldilocks" result with early initiation of moderate hypothermia for prolonged periods has shown the best outcomes[47].

Hypothermia in the stroke population

Investigation into the use of hypothermia treatment for ischemic stroke was first documented in 1987 as reducing neuronal death. Approximately 87% of all strokes, one of the leading causes of death and disability in the world, are ischemic[52]. Therapeutic hypothermia has been slowly accepted as one of the most reliable neuroprotective therapies for several cerebral disorders including stroke[53] [54]. Any improvement in the early outcome of ischemic stroke can lead to earlier entry to rehabilitation programs and eventual outcome and quality of life.

Like the pathophysiological effects discussed above, it is felt that hypothermia improves outcome of stroke via reduction in secondary cell damage. To date, numerous pre-clinical studies have shown that cooling affects multiple pathways at various stages of ischemic stroke (54). In the early stage of stage of ischemia, disruption of ionic homeostasis results in release of excitatory neurotransmitters due to increased intracellular calcium and release of excitatory neurotransmitters. Downstream, effects such as mitochondrial dysfunction leads to increased reactive oxygen species (ROS) generation[55].

Cold induced protein is another factor that may affect the neuroprotective effects of hypothermia[56]. Sun, et al[57] studied cold-inducible RNA-binding protein (CIRBP) and cold-inducible RNA-binding motif protein 3 (RBM3) as the major cold induced proteins produced. Hypothermia was then found to activate the expression of CIRBP [57]. Multiple studies found the expression of CIRBP could exert protective effects against oxidative stress and apoptosis[58] [59] [60].

The secondary effects of ischemia and more neuronal death includes apoptosis, oxidative stress, excitotoxic and inflammatory pathways[61]. Therapeutic hypothermia is thought to affect almost every one of these pathways and thus its robust protective effect[62]. Thus, therapeutic hypothermia is a became and continues to be looked as a promising and attractive therapy for ischemic stroke neurological minimization.

Outcome Studies – Acute phase

Therapeutic cooling has been documented to decrease brain oxygen consumption and glucose metabolism by about 5% per degree Celsius[63], while also preserving high- energy phosphate compounds, such as ATP, and maintaining tissue pH preventing acidosis[64]. Therapeutic hypothermia has also been shown to "prevent the accumulation or release of excitotoxic amino acids such as glutamate[63]" with obvious presumed benefit.

Finally, hypothermia was demonstrated to attenuate "ischemia-induced downregulation of GluR2 and would thus expect to reduce toxic calcium influx through this channel'[65].

Subacute Phase

The time of secondary injury is thought to occur between one and seven days after ischemic stroke[64]. Hypothermia is felt to affect both the intrinsic and extrinsic (cell receptors) effects of neuronal injury. Cooling was found to suppress the intrinsic (mitochondrial) pathway by regulating the expression of BCL-2 family members, reducing cytochrome C release and decreasing caspase activation [58]. The extrinsic pathway was improved by suppress the expression of both apoptosis-inducing death receptors FAS, and its ligand FASL[63]. A recently reported mechanism includes the role of dynamin-1, which is a protein described in exocytosis and synaptic transmission. "Dynamin is also upregulated in the brain in stroke models and its deficiency or inhibition is protective[66]." Therapeutic hypothermia was found to reduce dynamin expression.

Chronic Stage

The final question is whether hypothermia might affect recovery and repair mechanisms that occur in the brain long after the acute and subacute stages of injury. In the chronic stage, it was demonstrated that "endogenous restorative processes are activated, leading to neurogenesis and synaptogenesis[67]." Xiong et al[68], reported that therapeutic hypothermia was reported to enhance both maturation of neural progenitor cells and proliferation of neural stem cells, which can promote post-ischemic neurogenesis and synaptogenesis. Additionally, one report [64] showed that hypothermia "prevents post-ischemic reactive gliosis and glial scar formation."

Outcome studies

In studies of large animals first hypothermia was proven able and safe. Wang[69] found induced hypothermia in brain tissue of rhesus monkeys within 10 min, and the lowest cerebral temperature could be reduced to 33.9C. During the procedure, the vital signs of experimental animals were stable, and no adverse reaction such as brain edema and vasospasm occurred[69]. In 2016, Mattingly[70] and colleagues developed a model of middle cerebral artery occlusion in swine with an aneurysm clip. IA-SCI was induced by placing a dual lumen balloon occlusion catheter in the ipsilateral common carotid artery during reperfusion. The hypothermia induction lowered the cerebral hemisphere temperature to 30C within 25 min and found this

significantly reduced infarct volume on magnetic resonance imaging[70].

Recently, Caroff and colleagues[71], found that continuous infusion of hypothermic saline (4.5C) for 25 minutes at a rate of 22 ml per minute lowered the ipsilateral brain temperature to 31–32C. "Subsequent imaging examinations revealed that this method reduced the final infarct volume down to less than one tenth[71]".

The first study describing the safety and feasibility of IA-SCI in humans appeared in 2010 with 18 patients and 10 min of cooling with hypothermic saline[72]. Temperature was reduced by 0.84C with no adverse effects. In a pilot study of 26 patients with acute ischemic stroke, hypothermia applied within 8 hours cooling ischemic brain tissue by at least 2 degrees C by infusing 50 ml of cold isotonic saline[73]. No complications occurred. After this safety study, a prospective study of patients who had thrombectomy alone vs thrombectomy plus hypothermia showed "reduced the infarct volume, and also promoted the proportion of functional independence at 90 days numerically[74]". As a result of this pilot study, two larger studies are ongoing.

Hypothermia in Traumatic Brain Injury

Traumatic brain injury is the primary cause of worldwide morbimortality in young people (<45 years old)[75]. The annual incidence of TBI in the USA has been estimated to be 1.4 million cases, with 50,000 related deaths[76]. As stated above, a series of secondary pathophysiological mechanisms, which increase and perpetuate the damage caused by the initial insult. The mechanisms of this secondary damage are cerebral ischemia and hypoxia, excitotoxicity, inflammation, oxidative stress, metabolic dysfunction, seizures, brain edema and intracranial pressure (ICP) elevation, namely, intracranial hypertension (IH), through diminished brain perfusion pressure. IH is one of the clearest major determinants of outcome[77]. Prophylactic hypothermia therapy is believed to attenuate early cerebral inflammation and inflammatory cascades as a means of neuroprotection, evidence of which is measured through primary and secondary outcomes in several clinical trials[78]. Studies also demonstrated hypothermia could reduce intracranial pressure[79].

Clinical outcomes have been inconsistent. In a guideline review in 2017, level II B recommendations from the Brain Trauma Foundation did not support early or short- term (within 48 hours of injury) prophylactic hypothermia for patients with diffuse injury due to low-quality evidence[80 81]. However, in smaller studies, better outcomes were seen. Marion et al. in a 1997 published a randomized study involving 84 patients with severe TBI who were treated using mild hypothermia (33°C for 24 h). "There was a significantly better neurologic recovery at 3 months and at 6 months among the patients with GCS scores of 5–7 at the time of admission to the hospital[82]". Clifton et al,[83] published two studies that showed that late hypothermia had no impact on outcome. A 2009 Cochrane review included 23 trials and 1,614 patients with the following criteria: early hypothermia, target temperatures of 35°C for at least 12 h and the need for hospitalization[84]. Authors concluded that patients treated with hypothermia had better results with mortality and neurologic outcomes. However, this association was statistically significant in studies only with poor methodological quality. Andresen looked at 20 patients for cooling after TBI. Their target was to reduce intracranial hypertension. They found in patients with intracranial hypertension upon their intervention, the ICP levels were 23 mmHg [19–24; IQR] before hypothermia versus 13 mmHg [10.3–24; IQR] during hypothermia (p=0.003)[78].

Conclusions

From published case reports, pilot studies, and animal data, the use of therapeutic hypothermia in the setting of neurotrauma deserves further study. Could therapeutic hyperthermia become the standard intervention in all acute episodes of neurotrauma?

Only time and the outcome of future studies will tell. However, the potential promise of preservation or even return of lost neurological function after acute neurotrauma using TH is both intriguing and exciting. Therefore, we support the initiation of future studies. Additionally, the authors have proposed and submitted an IRB approved large multi- center study protocol to the national Institutes of Health. The study would investigate the outcomes of applying TH to patients after acute SCI using novel techniques and large patient groups. Hopefully, if funded the study will carry the weight and power necessary to answer the question proposed on whether TH should be used as standard treatment at all SCI centers when treating acute injuries of this type.

References

1. Babe J, Delgado F. Otogenous cerebral abscess treated by surgical intervention and hibernation. Acta oto-rino-laringologica ibero-americana. 1956;7:212-220
2. Henderson AR Temple F. Uncomfortable crusader and Harbinger of human refrigeration 1895-1963. 1963;J Neurosurg 20:627-634.
3. Zdravev P. Treatment of cerebral hernia following surgery of an otogenous brain abscess. Les Annales d'oto-laryngologie. 1951;68:201-205.
4. Busto R, Dietrich WD, Globus MY, Ginsberg MD. The importance of brain temperature in cerebral ischemic injury. Stroke. 1989;20:1113-1114.
5. Metz C, Holzschuh M, Bein T, Woertgen C, Frey A, Frey I, Taeger K, Brawanski A. Moderate hypothermia in patients with severe head injury: cerebral and extracerebral effects. J Neurosurg. 1996;85:533-541.
6. Clifton GL, Allen S, Barrodale P, Plenger P, Berry J, Koch S, Fletcher J, Hayes RL, Choi SC. A phase II study of moderate hypothermia in severe brain injury. J Neurotrauma. 1993;10:263-271; discussion 273.
7. Faridar A, Bershad EM, Emiru T, Iaizzo PA, Suarez JI, Divani AA. Therapeutic hypothermia in stroke and traumatic brain injury. Frontiers in Neurology. 2011;2:80
8. Sessler DI. Temperature monitoring and perioperative thermoregulation. Anesthesiology. 2008;109:318-338.
9. Jessen K. An assessment of human regulatory nonshivering thermogenesis. Acta anaesthesiologica Scandinavica. 1980;4:138-143.
10. Yenari M, Wijman C, Steinberg G. Effects of hypothermia on cerebral metabolism, blood flow, and autoregulation. In: Mayer S, Sessler D (eds) Therapeutic hypothermia. Marcel Dekker, New York. 2008;141-178
11. Varon J, Acosta P. Therapeutic hypothermia: past, present, and future. Chest. 2008;133:1267-1274.
12. Martinez-Arizala A, Green B (1992) Hypothermia in spinal cord injury. J Neurotrauma 9:S497-S505
13. Yu C, Jimenez O, Marcillo A, Weider B, Bangerter K, Dietrich W, Castro S, Yezierski R. Beneficial effects of modest systemic hypothermia on locomotor function and histopathological damage following contusion-induced spinal cord injury in rats. J Neurosurg (Spine). 2000;93: 1 Suppl 85–93
14. Chatzipantelli K, Yanagawa Y, Marcillo A, Kraydieh S, Dietrich W (2000) Posttraumatic hypothermia reduces polymorphonuclear leukocyte accumulation following spinal cord injury in rats. J Neurotrauma 17:321-332
15. Westergren H, Farooque M, Olsson Y, Holtz A (2000) Motor function changes in the rat following severe spinal cord injury. Does treatment with moderate systemic hypothermia improve functional outcome? Acta Neurochir (Wien) 142:567-573
16. Marsala M, Sorkin L, Yaksh T. Transient spinal ischemia in rat: Characterization of spinal cord blood flow, extracellular amino acid release, and concurrent histopathological damage. J Cereb Blood Flow Metab. 1994;14(4):604-14. Doi:10.1038/jcbfm https://pubmed.ncbi.nlm.nih.gov/8014207/
17. You JS, Kim JY, Yenari MA. Therapeutic hypothermia for stroke: Unique challenges at the bedside. Front Neurol. 2022 Oct 3;13:951586. Doi: 10.3389/fneur.2022.951586. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9575992/
18. Bernard SA, Mac CJB, Buist M. Experience with prolonged induced hypothermia in severe head injury. Critical Care. 1999;3:167-172.
19. Sunde K, Pytte M, Jacobsen D, Mangschau A, Jensen LP, Smedsrud C, Draegni T, Steen PA. Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. Resuscitation 2007;73:29-39.
20. Seule M, Muroi C, Sikorski C, Hugelshofer M, Winkler K, Keller E. Therapeutic hypothermia reduces middle cerebral artery flow velocity in patients with severe aneurysmal subarachnoid hemorrhage. Neurocritical care. 2014;20(2):255-62. Doi: 10.1007/s12028-013-9927-x.
21. Todd MM, Hindman BJ, Clarke WR, Torner JC (2005) Mild intraoperative hypothermia during surgery for intracranial aneurysm. N Engl J Med 352:135-145
22. Sherman AL, Wang MY. Hypothermia as a clinical neuroprotectant. Phys Med Rehabil Clin N Am. 2014 Aug;25(3):519-29, vii. Doi: 10.1016/j.pmr.2014.04.003. https://pubmed.ncbi.nlm.nih.gov/25064786/.
23. Vedantam A, Levi AD. Hypothermia for Acute Spinal Cord Injury. Neurosurg Clin N Am. 2021 Jul;32(3):377-387. Doi: 10.1016/j.nec.2021.03.009 https://pubmed.ncbi.nlm.nih.gov/34053725/
24. Polderman KH, Callaghan J. Equipment review: cooling catheters to induce therapeutic hypothermia? Crit Care. 2006;10(6):234. Doi: 10.1186/cc5023 https://pubmed.ncbi.nlm.nih.gov/17096865/

25. Jain A, Gray M, Slisz S, Haymore J, Badjatia N, Kulstad E. Shivering Treatments for Targeted Temperature Management: A Review. J Neurosci Nurs. 2018 Apr;50(2):63-67. Doi: 10.1097/JNN.0000000000000340. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5882245/
26. Blondin NA. Diagnosis and management of periodic hypothermia. Neurol Clin Pract.2014 Feb;4(1):26-33. Doi: 10.1212/01.CPJ.0000437350.47610.3a https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5765588/
27. Kranke P, Eberhart L, Roewer N, Tramer M (2002) Pharmacologic treatment of postoperative shivering: a quantitative systematic review of randomized controlled trials. Anesth Analg 2002;94:453-460.
28. Cappuccino A, Bisson L, Carpenter B, Marzo J, Dietrich W, Cappuccino H. The use of systemic hypothermia for the treatment of an acute cervical spinal cord injury in a professional football player. Spine. 2010;35:E57-E62.
29. Albin M, White R, Acosta-Rica G, Yashon D. Study of functional recovery produced by delayed localized cooling of spinal cord injury in primates. J Neurosurg. 1968;29:113-120.
30. Albin M, White R, Yashon D, Harris L (1969) Effects of cooling on spinal cord trauma.J Trauma. 1969;9:1000-1008.
31. Zhu L. Hypothermia Used in Medical Applications for Brain and Spinal Cord Injury Patients. Adv Exp Med Biol. 2018;1097:295-319. Doi: 10.1007/978-3-319-96445-4_16. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9575992/
32. Bracken MB, Shepard MJ, Collins WF, Holford TR, Young W, Baskin DS, Eisenberg HM, Flamm E, Leo-Summers L, Maroon J, et al. A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury. Results of the Second National Acute Spinal Cord Injury Study. N Engl J Med. 1990;322:1405-1411.
33. Bracken MB, Shepard MJ, Collins WF, Jr., Holford TR, Baskin DS, Eisenberg HM, Flamm E, Leo-Summers L, Maroon JC, Marshall LF, et al. Methylprednisolone or naloxone treatment after acute spinal cord injury: 1-year follow-up data. Results of the second National Acute Spinal Cord Injury Study. J Neurosurg.1992;76:23-31.
34. Bracken MB, Shepard MJ, Hellenbrand KG, Collins WF, Leo LS, Freeman DF, Wagner FC, Flamm ES, Eisenberg HM, Goodman JH, et al. Methylprednisolone and neurological function 1 year after spinal cord injury. Results of the National Acute Spinal Cord Injury Study. J Neurosurg. 1985;63:704-713.
35. Bracken MB, Shepard MJ, Holford TR, Leo-Summers L, Aldrich EF, Fazl M, Fehlings M, Herr DL, Hitchon PW, Marshall LF, Nockels RP, Pascale V, Perot PL, Jr., Piepmeier J, Sonntag VK, Wagner F, Wilberger JE, Winn HR, Young W. Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury. Results of the Third National Acute Spinal Cord Injury Randomized Controlled Trial. National Acute Spinal Cord Injury Study. JAMA 1994;277:1597-1604.
36. Hurlbert R (2001) The role of steroids in acute spinal cord injury: an evidence-based analysis. Spine 26:S55.
37. Hugenholtz H, Cass DE, Dvorak MF, Fewer DH, Fox RJ, Izukawa DM, Lexchin J, Tuli S, Bharatwal N, Short C. High-dose methylprednisolone for acute closed spinal cord injury--only a treatment option. Can J Neurol Sci. 2002;29:227-235.
38. Cappuccino A, Bisson LJ, Carpenter B, Snyder, Cappuccino H. Systemic Hypothermia as Treatment for an Acute Cervical Spinal Cord Injury in a Professional Football Player: 9-Year Follow-Up. Am J Ortho. 2017 Mar/Apr;E79-82.
39. Martinez-Arizala A, Green B. Hypothermia in spinal cord injury. J Neurotrauma.1992;9:S497-S505.
40. Dietrich WD, Levi AD, Wang M, Green BA. Hypothermic treatment for acute spinal cord injury. Neurotherapeutics. 2011 Apr;8(2):229-39. Doi: 10.1007/s13311-011- 0035-3. https://pubmed.ncbi.nlm.nih.gov/21416406/
41. Chatzipantelli K, Yanagawa Y, Marcillo A, Kraydieh S, Dietrich W. Posttraumatic hypothermia reduces polymorphonuclear leukocyte accumulation following spinal cord injury in rats. J Neurotrauma. 2000;17:321-332.
42. Pearse D, Lo T, Cho K, Lynch M, Garg M, Marcillo A, Sanchez A, Cruz Y, Dietrich W. Histopathological and behavioral characterization of a novel cervical spinal cord displacement contusion in the rat. Neurotrauma. 2005;22:680-702.
43. Meyer O, Tilson H, Byrd W, Riley M (1979) A method for the routine assessment of fore- and hindlimb strength of rats and mice. Neurobehav Toxicol. 1979;1:233-236.
44. Hosier, H., Peterson, D.N., Tsymbalyuk, O., Keledjian, K., Smith, B., Ivanova, S., Gerzanich, V., Popovich, P.G., & Simard, J.M. A Direct Comparison of Three Clinically Relevant Treatments in a Rat Model of Cervical Spinal Cord Injury. Journal of Neurotrauma. 2015; 32, 1633 - 1644.
45. Xu X, Li N, Zhu L, Zhou Y, Cheng H. Beneficial effects of local profound hypothermia and the

possible mechanism after experimental spinal cord injury in rats. J Spinal Cord Med. 2016;39(2):220-8.
Doi: 10.1179/2045772315Y.0000000051
https://pubmed.ncbi.nlm.nih.gov/26322652/

46. Jorge A, Fish EJ, Dixon CE, Hamilton KD, Balzer J, Thirumala P. The Effect of Prophylactic Hypothermia on Neurophysiological and Functional Measures in the Setting of Iatrogenic Spinal Cord Impact Injury. World Neurosurg. 2019 Sep;129:e607-e613.
Doi:10.1016/j.wneu.2019.05.229.
https://pubmed.ncbi.nlm.nih.gov/31158549/
47. Ransom SC, Brown NJ, Pennington ZA, Lakomkin N, Mikula AL, Bydon M, Elder BD. Hypothermia Therapy for Traumatic Spinal Cord Injury: An Updated Review. J Clin Med. 2022 Mar 13;11(6):1585. Doi: 10.3390/jcm11061585.
https://pubmed.ncbi.nlm.nih.gov/35329911/
48. Levi A, Green B, Wang M, Dietrich D, Brindle T, Vanni S, Casella G, Elhammady G, Jagid J. Clinical application of modest hypothermia after spinal cord injury. J Neurotrauma. 2009;26:407-415.
49. Dididze M, Green BA, Dietrich WD, Vanni S, Wang MY, Levi AD. Systemic hypothermia in acute cervical spinal cord injury: a case-controlled study. Spinal Cord. 2013 May;51(5):395-400.
Doi: 10.1038/sc.2012.161.
https://pubmed.ncbi.nlm.nih.gov/23247015/
50. Shin HK, Park JH, Roh SW, Jeon SR. Meta-Analysis on the Effect of Hypothermia in Acute Spinal Cord Injury. Neurospine. 2022 Sep;19(3):748-756.
Doi: 10.14245/ns.2244444.222
https://pubmed.ncbi.nlm.nih.gov/36203299/
51. Al-Nashash H, Al AH. Neuroprotective Role of Hypothermia in Acute Spinal Cord Injury. Biomedicines. 2022 Jan 4;10(1):104. Doi: 10.3390/biomedicines10010104
https://pubmed.ncbi.nlm.nih.gov/35052784/
52. Liu A, Zhang Z, Li A, Xue J, Effects of hypothermia and cerebral ischemia on cold-inducible RNA-binding protein mRNA expression in rat brain. Brain Res 2010:1347, 104–110.
53. van der Worp HB, Macleod MR, Bath PM, Demotes J, Durand-Zaleski I, Gebhardt B, Gluud C, Kollmar R, Krieger DW, Lees KR, Molina C, Montaner J, Roine RO, Petersson J, Staykov D, Szabo I, Wardlaw JM, Schwab S, Euro H. Y. P. i., EuroHYP-1: European multicenter, randomized, phase III clinical trial of therapeutic hypothermia plus best medical treatment vs. best medical treatment alone for acute ischemic stroke. Int J Stroke 2014;9, 642–645.
54. Yenari MA, Han HS, Neuroprotective mechanisms of hypothermia in brain ischaemia. Nat Rev Neurosci 2012;13, 267–278.
55. González-Ibarra FP, Varon J, López-Meza EG. Therapeutic hypothermia: critical review of the molecular mechanisms of action. Front Neurol. 2011 Feb 3;2:4.
Doi: 10.3389/fneur.2011.00004
https://pubmed.ncbi.nlm.nih.gov/21331282/
56. Wu L, Wu D, Yang T, Xu J, Chen J, Wang L, Xu S, Zhao W, Wu C, Ji X. Hypothermic neuroprotection against acute ischemic stroke: The 2019 update. J Cereb Blood Flow Metab. 2020 Mar;40(3):461-481.
57. Sun YJ, Ma S, Fan B, et al. Therapeutic hypothermia protects photoreceptors through activating Cirbp pathway. Neurochem Int 2019; 126: 86–95.
58. Liu J, Xue J, Zhang H, et al. Cloning, expression, and purification of cold inducible RNA-binding protein and its neuroprotective mechanism of action. Brain Res 2015; 1597: 189–195.
59. Li S, Zhang Z, Xue J, et al. Cold-inducible RNA binding protein inhibits H(2)O(2)- induced apoptosis in rat cortical neurons. Brain Res 2012; 1441: 47–52.
60. Zhuang RJ, Ma J, Shi X, et al. Cold-inducible proteinRBM3 protects UV irradiation- induced apoptosis in neuroblastoma cells by affecting p38 and JNK pathways and Bcl2 family proteins. J Mol Neurosci 2017; 63: 142–151.
61. Tuo QZ, Zhang ST, Lei P. Mechanisms of neuronal cell death in ischemic stroke and their therapeutic implications. Med Res Rev. 2022;Jan;42(1):259-305.
62. Wu C, Zhao W, An H, et al. Safety, feasibility, and potential efficacy of intraarterial selective cooling infusion for stroke patients treated with mechanical thrombectomy. J Cereb Blood Flow Metab 2018;38: 2251–2260.
63. Kurisu K, Kim JY, You J, Yenari MA. Therapeutic Hypothermia and Neuroprotection in Acute Neurological Disease. Curr Med Chem. 2019;26(29):5430-5455.
64. Kurisu K, Yenari MA. Therapeutic hypothermia for ischemic stroke; pathophysiology and future promise. Neuropharmacology. 2018;May 15;134(Pt B):302-309.
65. Hemmen TM, Lyden PD. Hypothermia after acute ischemic stroke. J Neurotrauma.2009 Mar;26(3):387-91.
66. Kim JY, Kim N, Lee JE, Yenari MA. Hypothermia Identifies Dynamin as a Potential Therapeutic Target in Experimental Stroke. Ther Hypothermia Temp Manag. 2017 Sep;7(3):171-177.
Doi: 10.1089/ther.2017.0005.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5610406/
67. Kernie SG, Parent JM. Forebrain neurogenesis

after focal Ischemic and traumatic brain injury. Neurobiol Dis. 2010 Feb;37(2):267-74. Doi: 10.1016/j.nbd.2009.11.002. https://pubmed.ncbi.nlm.nih.gov/19909815/

68. Xiong M, Cheng GQ, Ma SM, Yang Y, Shao XM, Zhou WH. Post-ischemic hypothermia promotes generation of neural cells and reduces apoptosis by Bcl-2 in the striatum of neonatal rat brain. Neurochem Int. 2011 May;58(6):625-33. Doi: 10.1016/j.neuint.2011.01.026. https://pubmed.ncbi.nlm.nih.gov/21300124/
69. Wang B, Wu D, Dornbos Iii D, Shi J, Ma Y, Zhang M, Liu Y, Chen J, Ding Y, Luo Y, Ji X. Local cerebral hypothermia induced by selective infusion of cold lactated ringer's: a feasibility study in rhesus monkeys. Neurol Res. 2016 Jun;38(6):545-52. Doi: 10.1080/01616412.2016.1187827. https://pubmed.ncbi.nlm.nih.gov/27320250/
70. Mattingly TK, Denning LM, Siroen KL, et al. Catheter based selective hypothermia reduces stroke volume during focal cerebral ischemia in swine. J Neurointerv Surg 2016; 8: 418–422.
71. Caroff J, King RM, Mitchell JE, et al. Focal cooling of brain parenchyma in a transient large vessel occlusion model: proof-of-concept. J Neurointerv Surg. Epub ahead of print 30 July 2019. Doi: 10.1136/neurintsurg-2019-015179.
72. Choi JH, Marshall RS, Neimark MA, et al. Selective brain cooling with endovascular intracarotid infusion of cold saline: a pilot feasibility study. AJNR Am J Neuroradiol 2010; 31: 928–934.
73. Chen J, Liu L, Zhang H, et al. Endovascular hypothermia in acute ischemic stroke: pilot study of selective intra-arterial cold saline infusion. Stroke 2016; 47:1933– 1935.
74. Myburgh JA, Cooper DJ, Finfer SR, Venkatesh B, Jones D, Higgins A, et al.Epidemiology and 12-month outcomes from traumatic brain injury in australia and new zealand. J Trauma. 2008;64:854–862. Doi: 10.1097/TA.0b013e3180340e77. https://pubmed.ncbi.nlm.nih.gov/18404048/
75. Langlois JA, Rutland-Brown W, Wald MM. The epidemiology and impact of traumatic brain injury: a brief overview. J Head Trauma Rehabil. 2006;21:375–378. Doi: 10.1097/00001199-200609000-00001. https://pubmed.ncbi.nlm.nih.gov/16983222/
76. Vik A, Nag T, Fredriksli OA, Skandsen T, Moen KG, Schirmer-Mikalsen K, et al. Relationship of "dose" of intracranial hypertension to outcome in severe traumatic brain injury. J Neurosurg. 2008;109:678–684. Doi: 10.3171/JNS/2008/109/10/0678. https://pubmed.ncbi.nlm.nih.gov/18826355/
77. Miller JD, Butterworth JF, Gudeman SK, Faulkner JE, Choi SC, Selhorst JB, et al. Further experience in the management of severe head injury. J Neurosurg. 1981;54:289–299. Doi: 10.3171/jns.1981.54.3.0289. https://pubmed.ncbi.nlm.nih.gov/7463128/
78. Andresen M, Gazmuri JT, Marín A, Regueira T, Rovegno M. Therapeutic hypothermia for acute brain injuries. Scand J Trauma Resusc Emerg Med. 2015 Jun 5;23:42. Doi: 10.1186/s13049-015-0121-3 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4456795/
79. Henderson WR, Dhingra VK, Chittock DR, Fenwick JC, Ronco JJ. Hypothermia in the management of traumatic brain injury: A systematic review and meta-analysis. Intensive care medicine. 2003 Oct;29:1637-44.
80. Carney N, Totten AM, O'Reilly C, Ullman JS, Hawryluk GW, Bell MJ, Bratton SL, Chesnut R, Harris OA, Kissoon N, Rubiano AM. Guidelines for the management of severe traumatic brain injury. Neurosurgery. 2017 Jan 1;80(1):6-15.
81. Cooper DJ, Nichol AD, Bailey M, Bernard S, Cameron PA, Pili-Floury S, Forbes A, Gantner D, Higgins AM, Huet O, Kasza J. Effect of early sustained prophylactic hypothermia on neurologic outcomes among patients with severe traumatic brain injury: the POLAR randomized clinical trial. Jama. 2018 Dec 4;320(21):2211-20. https://pubmed.ncbi.nlm.nih.gov/30357266/
82. Marion DW, Penrod LE, Kelsey SF, Obrist WD, Kochanek PM, Palmer AM, Wisniewski SR, DeKosky ST. Treatment of traumatic brain injury with moderate hypothermia. N Engl J Med. 1997 Feb 20;336(8):540-6. Doi: 10.1056/NEJM199702203360803. https://pubmed.ncbi.nlm.nih.gov/9023090/
83. Clifton, G.L., Valadka, A., Zygun, D., Coffey, C.S., Drever, P., Fourwinds, S., Janis, L.S., Wilde, E., Taylor, P., Harshman, K. and Conley, A., Very early hypothermia induction in patients with severe brain injury (the National Acute Brain Injury Study: Hypothermia II): a randomised trial. The Lancet Neurology, 201110(2), pp.131-139.
84. Sydenham E, Roberts I, Alderson P. Hypothermia for traumatic head injury. Cochrane Database Syst Rev. 2009;2:CD001048 https://pubmed.ncbi.nlm.nih.gov/19160187/