Therapeutic hypothermia and targeted temperature management for traumatic brain injury: Experimental and clinical experience

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Abstract:
Traumatic brain injury (TBI) is a worldwide medical problem, and currently, there are few therapeutic interventions that can protect the brain and improve functional outcomes in patients. Over the last several decades, experimental studies have investigated the pathophysiology of TBI and tested various pharmacological treatment interventions targeting specific mechanisms of secondary damage. Although many preclinical treatment studies have been encouraging, there remains a lack of successful translation to the clinic and no therapeutic treatments have shown benefit in phase 3 multicenter trials. Therapeutic hypothermia and targeted temperature management protocols over the last several decades have demonstrated successful reduction of secondary injury mechanisms and, in some selective cases, improved outcomes in specific TBI patient populations. However, the benefits of therapeutic hypothermia have not been demonstrated in multicenter randomized trials to significantly improve neurological outcomes. Although the exact reasons underlying the inability to translate therapeutic hypothermia into a larger clinical population are unknown, this failure may reflect the suboptimal use of this potentially powerful therapeutic in potentially treatable severe trauma patients. It is known that multiple factors including patient recruitment, clinical treatment variables, and cooling methodologies are all important in yielding beneficial effects. High-quality multicenter randomized controlled trials that incorporate these factors are required to maximize the benefits of this experimental therapy. This article therefore summarizes several factors that are important in enhancing the beneficial effects of therapeutic hypothermia in TBI. The current failures of hypothermic TBI clinical trials in terms of clinical protocol design, patient section, and other considerations are discussed and future directions are emphasized.

Keywords:
Clinical trials, fever, pathophysiology, targeted temperature management, therapeutic hypothermia, traumatic brain injury

Introduction

Traumatic brain injury (TBI) is a serious worldwide health problem that includes mild, moderate, and severe injuries. Within the United States, there are over 1.7 million new patients each year who sustain some type of TBI with a vast majority of those patients having mild TBI (mTBI) or concussive insults. Depending on the location of the primary impact and injury severity, patients can be left with a spectrum of functional problems including sensorimotor, cognitive, and a range of postconcussive symptoms. The pathophysiology of TBI is complex and previous research has clarified a number of secondary injury mechanisms important in the generation of structural and functional deficits in patients. These injury mechanisms include excitotoxicity, apoptosis, free radical generation, as well as inflammatory processes that

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contribute to neural dysfunction, cell death, axonal and vascular damage, and circuit dysfunction.[7,8] Based on this complex pathophysiology, a spectrum of pharmacological interventions have been developed and tested using a variety of preclinical models with different degrees of success.[9,10] To date, however, no therapeutic interventions have successfully improved behavioral outcomes in multicenter phase 3 clinical trials for TBI.[11-13] For example, in recent clinical testing, the neuroprotective agents progesterone and erythropoietin both failed to improve outcomes in well-designed multicenter clinical trials.[11,15-18]

Profound focal levels of hypothermia have been known for many years to be effective in reducing brain edema and improving functional outcomes in models of TBI.[16-18] However, more recent preclinical studies also demonstrated that relatively mild reductions in systemic brain temperature were also neuroprotective in models of global and focal cerebral ischemia.[19-23] TBI studies have been initiated to test the benefits of mild systemic hypothermia on histopathological and behavioral outcomes.[24-34] Clifton et al. first utilized moderate hypothermia (30°C) in a rat moderate lateral fluid percussion injury (FPI) and showed that the induction of hypothermia before or soon after the primary insult improved motor function using beam-walking and beam-balance outcome measures.[25] Subsequently, Dietrich et al. reported that early posttraumatic cooling significantly reduced histopathological damage after moderate FPI.[35] In that study, a reduction of brain temperature to 30°C starting 5 min after TBI and extended for 3 h significantly reduced overall contusion volume as well as the frequency of dead neurons within the adjacent cerebral cortex [Figure 1].[35] Encouraging findings with posttraumatic hypothermia were also reported from other laboratories using different animal models with variable levels and durations of cooling.[30,36-37] Together, these preclinical studies showed that the early induction of mild-to-moderate hypothermia in models of both focal as well as diffuse TBI was beneficial in terms of a variety of histopathological outcomes and functional outcomes including cognitive assessment.[31,34,38-40]

Based on these encouraging findings from multiple research groups, a number of single institutional clinical studies using a relatively small number of subjects were initiated in severe TBI patients to test the beneficial effects of moderate systemic hypothermia [Figure 2].[46-51] Importantly, several of these clinical investigations reported that the induction of early hypothermia reduced abnormal elevations in intracranial pressure (ICP) as well as improved neurological function at chronic survival periods.[49] However, results from additional randomized controlled clinical trials resulted in conflicting findings.[53-55]

The first multicenter trial, National Acute Brain Injury Study: Hypothermia (NABIS: H) that involved a number of recruitment sites throughout the United States, failed to show beneficial effects in terms of improving functional outcomes.[56] Many questions emerged from this multicenter trial suggested that this negative finding might be due to a delay in initiating the cooling protocol as well as patient management protocols that may have varied between recruitment sites.[57] Although negative, overall hypothermia treatment appeared to work best in younger patients who were cooled early after the traumatic insult.[56] A second multicenter trial was initiated based on these observations where several changes in the treatment protocol were initiated.[58] Unfortunately, therapeutic hypothermia was again shown to be ineffective in this second multicenter trial, resulting in the study being stopped. Interestingly, *post hoc* analysis of the data sets from the two previous NABIS: H trials indicated that hypothermia might work best in the treatment group where patients had undergone early cooling combined with decompression.
In contrast to this observation, there appeared to be a lack of therapeutic efficacy in patients who had diffuse axonal injury and were cooled. Although the current literature including systematic reviews and meta-analyses does not support the routine use of hypothermia for the management of severe TBI in pediatric and adult patients, more recent studies suggest that specific patient populations may benefit from this experimental treatment. Over the last several years, there have been reports suggesting various explanations for the lack of efficacy of therapeutic hypothermia with severe TBI. Furthermore, considerable work has continued using preclinical TBI models to more clearly define the most critical factors that may be important when designing clinical trials for the use of therapeutic hypothermia. In this regard, variables including the therapeutic window, duration and level of cooling, as well as the rewarming protocol have been emphasized. Each of these factors is now appreciated to be highly relevant for maximizing the beneficial effects of hypothermic treatment, and these concepts need to be considered and integrated into the design of future clinical trials.

**Level of Hypothermia**

Studies initiated in the 1940s and 1950s for cardiac by-pass surgery utilized very profound levels of hypothermia to protect the heart and brain. As previously mentioned, encouraging preclinical studies for transient global cerebral ischemia first reported that more mild-to-moderate levels of systemic hypothermia were protective in reducing ischemic cell death as well as improving behavioral outcome measures. Indeed, it was discovered that in some circumstances, only a 1- or 2-degree difference in intra-ischemic brain temperature significantly altered the severity of hippocampal CA1 neuronal cell death. Based on these findings, moderate levels of systemic hypothermia were tested in several models of TBI. Early studies showed that hypothermic levels ranging from 30°C to 34°C were effective in improving a variety of clinically relevant outcomes. However, in terms of the potential use of systemic hypothermia in TBI patients, it was determined that reducing core temperature to levels below 33°C could potentially increase the frequency of risk factors, including changes in clotting factors, increased incidence of pneumonia and cardiac arrhythmias as well as reducing heart rate or blood pressure. Thus, in clinical studies including cardiac arrest, TBI, and spinal cord injury (SCI), levels of systemic hypothermia ranging from 33°C to 36°C have been commonly utilized. An important question remains whether lower levels of hypothermia might be more protective in the experimental or clinical setting under certain situations. This question is being currently addressed by utilizing more selective or focal-cooling strategies with new cooling devices.
patients reported that metabolic-targeted hypothermia treatment reduced metabolic rate to 50%–60% in contrast to testing a predetermined temperature target which would significantly reduce mortality.\[82\]

Recent findings, specifically from the cardiac arrest field, have suggested that possibly more mild levels of hypothermia may be just as effective as moderatecooling strategies.\[83\] For example, in the recent 33 versus 36 cardiac arrest study, Nielsen et al. reported that a postcardiac arrest patient population that was cooled to either 33°C or 36°C both showed similar behavioral outcomes.\[83\] This study emphasized that moderate levels of hypothermia previously reported to significantly improve outcomes after cardiac arrest may not be necessary to promote protection.\[84-86\] Several issues have subsequently been raised in the literature regarding this well-conducted multicenter cardiac arrest trial, including a significant delay in the initiation of cooling, the lack of consistently reaching cooling levels in the 33°C group, and a relatively rapid rewarming phase.\[87,88\] Thus, there is a continued need to consider optimal cooling levels and whether specific patient populations may benefit from specific levels of cooling depending on their condition and injury severity. Because TBI is also a very heterogeneous patient population, it will be important in future studies to develop diagnostic strategies including imaging and surrogate protein biomarker approaches to better select appropriate patients and to monitor temperature-sensitive injury cascades.\[89,90\] Such an approach would allow physicians to vary therapeutic treatments based on an individual’s specific status. Furthermore, because many patients have focal lesions that can be identified with high-resolution computed tomography or magnetic resonance imaging, it might be important in future investigations to consider more focal-cooling strategies for these patients.\[80,91\] This strategy would allow more profound levels of cooling to be utilized, thereby potentially producing more neuroprotective efficacy with reduced risk factors associated with cooling.

**Therapeutic Window**

One of the most important factors on whether a therapy can be successfully translated to the clinic is whether the delayed initiation of the therapy remains significantly protective in a preclinical study.\[82\] In the previous brain injury studies, investigators have administered treatments relatively early after the insult to evaluate the effects of new treatments on specific pathomechanisms as well as structural or behavioral outcomes.\[29,30,32,35,76\] In contrast, many of these studies have not included a systematic examination of whether a delayed treatment protocol remains effective several hours after injury. This is a critical factor when thinking about clinical translation since many TBI patients may not be brought into the emergency room or assessed by a clinician until hours after the primary insult. If a treatment can only work when administered before or at early postinjury periods, it may be difficult to translate that treatment protocol to the clinical arena.

In the area of therapeutic hypothermia, Markgraf et al. first evaluated the therapeutic window for therapeutic hypothermia after experimental TBI.\[33\] That study reported that significant beneficial effects of moderate hypothermia were seen when treatment was initiated as late as 90 min.\[93\] However, if cooling was initiated after that period of time, there was a lack of benefit in terms of behavioral outcomes. In contrast, other subsequent studies have reported that systemic hypothermia remains effective even when it is delayed up to 3–4 h after injury.\[92\] Importantly, the therapeutic window of hypothermia appears to be based on several factors including level of hypothermia, injury severity, specific injury model utilized, and whether the trauma is focal or diffuse. Nevertheless, in the clinic, cooling strategies are generally initiated as soon as possible to target early occurring secondary injury mechanisms.

One challenge for early cooling is the lack of safe and established strategies for rapid cooling. In some studies, the infusion of cold saline has been used to reduce core temperature in a rapid fashion.\[95\] Importantly, recent technological advances in the development of effective intravascular, surface, and other cooling approaches have reduced the delay in reaching hypothermia temperature targets.\[96-99\]

**Duration of Cooling**

Many early preclinical studies tested the beneficial effects of posttraumatic hypothermia using relatively restricted periods of cooling.\[29,30,32,35,100-102\] In early studies of TBI, for example, many published studies reported positive effects with relatively restricted duration.\[29,30,32,35,76\] Interestingly, studies from the transient and focal cerebral ischemia field have reported that restricted periods of cooling may only transiently protect against ischemic brain injury.\[103-105\] In a recent TBI study, Lu et al. demonstrated the beneficial effects of an extended period of selective brain cooling in a model of penetrating ballistic-brain injury. These and other observations have led to investigations to determine the optimal periods of cooling required to produce permanent benefits including clinically meaningful neurological improvements.\[106\] In previous hypothermia studies, TBI patients have also been cooled using a variety of durations ranging from 24 h up to several days after trauma.\[46,57,69,70,107-109\]

When considering the importance of cooling duration on traumatic outcome, one should also consider what...
secondary injury mechanisms are being targeted by the cooling protocol.\textsuperscript{[124,36,38,43,44,75,110-113]} Previous studies have reported that hypothermia can influence a number of injury mechanisms that are active at variable periods during the posttraumatic period.\textsuperscript{[114]} In this regard, injury mechanisms such as free radical formation and excitotoxicity are active fairly early after injury. In contrast, other important secondary mechanisms such as apoptotic cell death and inflammatory processes may be more delayed but remain active for days after injury. In terms of acute pathophysiological mechanisms, hypothermia initiated early after the insult and continued during the time when secondary injury mechanisms are active in the patient should therefore be considered.\textsuperscript{[21,27,31,75,115]} Thus, early cooling continued for up to several days after injury may be necessary to successfully target these injury cascades.

A second mechanism that is considered to be an important therapeutic target for TBI is the elevations in ICP.\textsuperscript{[6,48,49,70,71,107,108,116-118]} Many patients after moderate or severe TBI or other types of brain injury experience focal or diffuse brain swelling that can lead to increases in ICP that can be life threatening.\textsuperscript{[6,7,107]} The temporal pattern of ICP elevations can also be highly variable from patient to patient.\textsuperscript{[48]} Thus, it is important when developing a clinical hypothermia protocol to consider cooling or targeted temperature management being on board before or rapidly initiated when ICP elevations occur.\textsuperscript{[116,119,120]} Because early secondary injury mechanisms and delayed increases in ICP can each significantly affect patient outcomes, an optimal approach for the use of therapeutic hypothermia may be initiating cooling strategies as early as possible and extending them through the period of elevated ICP.\textsuperscript{[56,58,68,116,118,121]}

In this regard, several clinical studies have used early cooling protocols that were only sustained for a 24- or 48-h period and therefore may not have extended to the period of increased ICP.\textsuperscript{[58,70,29]} Some clinical studies that have utilized early and more prolonged cooling strategies have reported improvements in neurological outcomes in preclinical studies.\textsuperscript{[122,123]} In the study by Jhang et al., for example, extending the cooling period up to 5 days was reported to provide better neurological outcomes compared to a 2-day cooling protocol.\textsuperscript{[122]} Further, in a recent multicenter clinical trial where hypothermic treatment was delayed and only restricted to the period of ICP elevation, no long-term benefits on neurological outcomes were reported although ICP elevations appeared to be successfully managed with the targeted cooling treatment.\textsuperscript{[108,113]}

**Rewarming Phase**

Following a period of extended hypothermia, another important factor to maximize the benefits of cooling is using a relatively slow and controlled rewarming protocol.\textsuperscript{[6,124,125]} Rapid-rewarming strategies, especially following a prolonged period of cooling, have been reported not to be optimal in terms of improving long-term outcome.\textsuperscript{[126]} A study by Suehiro et al. reported that a slow-progressive cooling approach compared to rapid cooling was more effective in protecting against traumatically induced axonal damage commonly reported in experimental models of TBI.\textsuperscript{[127]} In another study that assessed a complicated model of TBI that included FPI combined with secondary hypoxia, slow but not rapid rewarming again produced the best effect in terms of behavioral outcomes.\textsuperscript{[124]} Impairments in cerebral vascular reactivity have been reported in TBI patients after rewarming from therapeutic hypothermia, leading to increased neuronal vulnerability.\textsuperscript{[128]} Although underlying mechanisms are not known, inadvertent cerebral hyperthermia has been suggested in some situations.\textsuperscript{[129]}

Based on these preclinical findings, recent clinical studies have developed established protocols for conducting therapeutic hypothermia in patients combined with a slow and controlled rewarming phase.\textsuperscript{[121,129]} In one clinical study that used therapeutic hypothermia to target severe SCI, for example, Levi et al. after 2 days of systematic therapeutic hypothermia (33°C) combined with slow rewarming was also used with encouraging results.\textsuperscript{[121]}

In operating room settings, slow rewarming after a surgical procedure may not be consistent with normal-operating procedures that commonly necessitate high throughput. Rapid rewarming, especially after a prolonged period of hypothermia, may stress vulnerable tissues leading to the aggravation of secondary injury mechanisms, including brain edema and other detrimental consequences.\textsuperscript{[6,130,131]} Further, it is important to emphasize that a rapid-rewarming protocol can lead to temperature overshoots and periods of posttreatment hyperthermia which also may be detrimental to long-term outcomes, especially when associated with an extended hypothermia treatment protocol.\textsuperscript{[88,128]}

**Gender**

A shortcoming of many preclinical studies is that only one gender is used to investigate traumatic pathomechanisms or new therapeutic interventions.\textsuperscript{[132,133]} In the area of TBI, for example, the majority of preclinical studies have been restricted to only male animals for a
number of stated or unstated reasons. However, in the clinical arena, it is clear that both sexes have TBIs and any sex-specific differences in the pathophysiology or potential treatment effects should be first evaluated before clinical translation.[3,134-136] Previous investigations have reported gender differences that may be important when attempting to translate new therapies to the clinic.[137-139] Early studies by Roof et al. showed that sex hormones including estrogen and progesterone were neuroprotective after TBI and therefore important when considering gender-specific differences in traumatic vulnerability.[139] In those and other studies, the removal of the ovaries before producing a TBI enhanced the vulnerability of the female brain, leading to increased contusion volumes and behavioral deficits compared to intact animals.[132,133] Bramlett et al. directly compared the effects of moderate FPI in both male and female rats and reported that female rats displayed smaller contusion volumes compared to males.[132] In addition, removing the ovaries several days before TBI increased tissue vulnerability, resulting in similar contusion volumes between both male and ovariectomized female rats. Together, these studies emphasize the importance of sex hormones in the pathophysiology of TBI and the potential benefits of hormonal treatments on neurological disorders such as stroke. These types of preclinical studies have also led to clinical trials where progesterone and other hormonal treatments have been tested after severe TBI.[140,141]

In terms of injury mechanisms, recent preclinical studies have emphasized gender differences in specific pathophysiological events following TBI.[137,138,142] In a recent study, for example, Villapol et al. reported significant differences in the neuroinflammatory response to TBI in male versus female rats.[142] In those studies, male rats were reported to show a more aggressive inflammatory response compared to female rats after TBI. The importance of gender in the effects of temperature modifications after brain injury has also been emphasized.[138,143-145] For example, in a model of neonatal hypoxia-ischemia, Smith et al. reported that the beneficial effect of therapeutic hypothermia differed between male and female.[145] In a TBI study, posttraumatic hypothermia was also reported to protect males but not intact females after moderate FPI.[138] However, ovariectomized females showed increased contusion volumes that were comparable to males and were protected by posttraumatic hypothermia. In contrast to hypothermia, other studies have shown that ovariectomized female rats are more affected by posttraumatic hyperthermia than intact female rats. In a study by Suzuki et al., posttraumatic hyperthermia in ovariectomized female rats resulted in a dramatic increase in diffuse axonal injury compared to intact females.[137] These preclinical findings are important as we continue to develop novel therapeutic agents and clinical protocols for the future TBI trials, where neuroprotective or reparative strategies are tested. It will be important to recruit adequate numbers of male and female patients in clinical trials to clarify the importance of sex in the therapeutic efficacy of experimental treatments.

**Heterogeneity of Traumatic Brain Injury Patient Population**

One of the major challenges in conducting clinical trials for severe TBI as well as other neurological disorders is the heterogeneity of the patient population.[97,146,147] Different types of TBI commonly occur in the general population, which include focal, diffuse, as well as a combination of both types of injuries. In addition, many severe TBI patients can experience multorgan injury that may also complicate treatment approaches. The acute severity and duration of clinical consequences after a brain injury can also be highly variable in patients undergoing mTBI or concussive insults. This potential heterogeneity therefore has to be taken into account when developing clinical trial protocols to test a new therapeutic treatment in TBI patients. For example, the temporal or regional profile of inflammatory cascades would be expected to significantly vary between patients with different degrees of pathological damage while exhibiting similar early neurological score assessments. Precision or specialized medical approaches are now being used to potentially reduce patient heterogeneity and improve treatment outcomes.

An important area of the current clinical research is the development of minimally invasive surrogate biomarkers including imaging and protein biomarkers which may help identify subsets of patients who may most benefit from a particular treatment.[146-151] In this regard, failure of previous stroke and TBI clinical trials have been suggested to be the result of enrolling highly heterogeneous patient populations. To respond to this apparent shortcoming in clinical trial design, studies are now utilizing more restricted inclusion and exclusion criteria to help recruit a more homogenous patient population. It is anticipated that such an approach may lead to a more successful translation of preclinical findings to the clinic.

**Posttraumatic Hyperthermia**

Periods of hyperthermia occur in a large number of stroke and trauma patients hours to days after the primary insult.[12,47,152-158] Importantly, preclinical and clinical studies have concluded that periods of posttraumatic hyperthermia may worsen outcome by aggravating secondary injury mechanisms, leading to increases in contusion volume, diffuse axonal injury, and ICP.[159,160] In an early preclinical study, Dietrich and Bramlett...
reported that an induced period of posttraumatic hyperthermia 24 h after TBI worsened histopathological damage and aggravated behavioral deficits compared to normothermic animals.\[163\] Similar to therapeutic hypothermia, periods of posttraumatic hyperthermia target multiple secondary injury mechanisms that are thought to contribute to the long-term consequences of TBI.\[20,153\] For example, published studies have reported that hyperthermia following brain injury aggravates patterns of excitotoxicity, free radical generation, apoptotic cell death, as well as a variety of inflammatory cascades. In terms of inflammation, Chatzipanteli et al. reported that an induced period of posttraumatic hyperthermia increased polymorphonuclear leukocyte extravasation into the vulnerable brain tissue associated with increases in tissue levels of pro-inflammatory cytokines.\[27\] These and other studies have led to the use of targeted temperature management protocols to inhibit periods of hyperthermia that are commonly observed in many TBI patients. In a recent clinical TBI study, Hifumi et al. reported that fever control management was preferable to mild hypothermia in reducing TBI-related mortality.\[162\] Indeed, targeted temperature management protocols are used in many clinical situations to reduce the incidence of hyperthermia in Intensive Care Unit patients following brain and SCI and to maintain normothermic conditions. Most recently, the importance of brain hyperthermia in models of mTBI or concussion has also been reported.\[163-165\] Sakurai et al. first demonstrated that increasing brain temperature to 39°C at the time of impact and continued for 4 h significantly increased histopathological damage compared to normothermic mTBI animals.\[164\] In a subsequent study, Titus et al. using a similar experimental protocol reported that hyperthermic mTBI led to the emergence of long-term cognitive problems which are not present in animals that underwent normothermic mTBI.\[160\] These studies are important because many individuals prone to concussion such as athletes or military personnel frequently undergo strenuous activities such as sports-related events or stressful activities that can lead to increased core and brain temperature. Indeed, a variety of clinical studies have been reported that individuals exercising specifically in warm climates can demonstrate significant elevations in jugular blood temperature above 39°C.\[166-168\] These studies emphasize that brain temperature at the time of a relatively mild impact may vary from individual to individual and potentially participate in the severity of functional consequences including postconcussive syndromes. Recent studies have reported that elevated mild hyperthermic mTBI significantly aggravates neuroinflammatory and microvascular responses compared to normothermia.\[165\] In addition to more severe TBI injuries, mTBI or concussive insults may also require targeted temperature management strategies to minimize the detrimental effects of these more common types of milder insults to the brain.

**Recent Clinical Trial Failure**

Previous and more recent multicenter trials using pharmacological compounds or therapeutic hypothermia...
for severe TBI have failed to show efficacy in large numbers of patients.\cite{11,14,15,56,57,60} Earlier clinical studies by Clifton and colleagues indicated that the early initiation of hypothermia as well as the patient population could be important factors in determining the benefits of hypothermia. Indeed, the heterogeneity of the TBI patient population has emphasized the importance of patient selection and recruitment in terms of demonstrating benefits from hypothermic therapy.\cite{60,70}

Recently, a large multicenter trial that used cooling to target increases in ICP also failed to show functional benefits of therapeutic hypothermia.\cite{108} In the Eurotherm 3235 trial, the investigators sought to utilize hypothermia only when evidence of increased ICP occurred in the patients.\cite{107,108} In this specific protocol, targeting early secondary pathophysiological mechanisms was therefore not included. Unfortunately, the clinical trial although showing a benefit in terms of attenuating ICP elevations did not demonstrate any long-term improvements in neurological outcomes.\cite{113} Mechanisms underlying the ultimate consequences of TBI are complicated and involve multiple injury cascades including early and later pathophysiological events.\cite{6,142} It will therefore be important in the future to develop and test clinical protocols that include both early- and prolonged-cooling strategies that extend past the period when ICP elevations remain present.\cite{40,121}

Ongoing studies are also incorporating more extended periods of cooling that again may provide better outcomes in specific patient populations.\cite{40,121} A recent study in Japan will be utilizing an extended-cooling strategy that includes both early and prolonged cooling. This trial will therefore target a variety of injury processes at extended posttraumatic periods and may therefore have the best chance of providing long-term outcomes.\cite{40}

A recent development in terms of clinical trials using therapeutic hypothermia for TBI is the HOPES trial.\cite{43,169} This trial is currently recruiting severe TBI patients from several institutions within the United States as well as Japan and China. Inclusion criteria include patients where early decompression surgery is required. The protocol involves early cooling with decompression surgery in severe TBI patients. The overall hypothesis is that cooling before the decompression surgery attenuates some of the detrimental effects of reperfusion injury that can occur when blood re-enters the ischemic area. Reperfusion injury has been studied extensively in the heart and involves a variety of injury mechanisms including free radical generation, glutamate neurotoxicity, and other injury mechanisms.\cite{45} Whether this particular targeted therapy in this specific TBI patient population will provide beneficial effects remains to be demonstrated.\cite{170}

**Pharmacologically Induced Hypothermia**

In addition to physical strategies for local or focal hypothermia, new investigations are clarifying the potential for pharmacologically induced hypothermia to also benefit patients with cerebral ischemia or TBI.\cite{171-175} Various research groups have identified drugs or compounds that target mechanisms underlying temperature homeostasis which may allow for an efficient pharmacological approach for inducing hypothermia. For example, compounds that target adenosine A1 receptors, opioid receptors, transient receptor potential (TRP) channels, and dopamine receptors have been reported to produce hypothermia.\cite{176-178} In neonatal rats, Gu et al. reported that the neurotensin receptor agonist HPI 201-induced hypothermia reduced neuronal damage and blood–brain barrier in a pediatric model of TBI [Figure 4].\cite{172} Alterations in the hypothermia regulatory set point or peripheral temperature sensitive channels are among the mechanisms underlying pharmacological hypothermia.\cite{179-181} An exciting future direction therefore could be the use of therapeutic hypothermia-inducing drugs in combination with passive-cooling strategies. This new approach could enhance the benefits of hypothermia in terms of accelerating the hypothermic phase and maximize neuroprotective benefits.

**Summary**

Although therapeutic hypothermia remains one of the most potent neuroprotective strategies investigated to date, it is clear from the current literature that there remain many challenges for successfully utilizing therapeutic hypothermia in severe TBI patients.\cite{65} Only through the continued translation of supportive preclinical data to the clinic will important advancements be made in this exciting field. Controlled, hypothesis-driven approaches are required to treat TBI patients with specialized targeted temperature management protocols that have a chance of improving outcomes. The potential use of therapeutic hypothermia in combination with FDA-approved therapeutic drugs also represents an exciting direction for continued research. The combination of therapeutic hypothermic and targeted temperature management approaches with pharmacotherapy to protect or repair the injured nervous system may lead to true improvements in long-term outcomes in this important clinical condition.

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Conflicts of interest

There are no conflicts of interest.

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