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Therapeutic Hypothermia and Targeted Temperature Management in Traumatic Brain Injury: Clinical Challenges for Successful Translation

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Abstract

The use of therapeutic hypothermia (TH) and targeted temperature management (TTM) for severe traumatic brain injury (TBI) has been tested in a variety of preclinical and clinical situations. Early preclinical studies showed that mild reductions in brain temperature after moderate to severe TBI improved histopathological outcomes and reduced neurological deficits. Investigative studies have also reported that reductions in post-traumatic temperature attenuated multiple secondary injury mechanisms including excitotoxicity, free radical generation, apoptotic cell death, and inflammation. In addition, while elevations in post-traumatic temperature heightened secondary injury mechanisms, the successful implementation TTM strategies in injured patients to reduce fever burden appear to be beneficial. While TH has been successfully tested in a number of single institutional clinical TBI studies, larger randomized multicenter trials have failed to demonstrate the benefits of therapeutic hypothermia. The use of TH and TTM for treating TBI continues to evolve and a number of factors including patient selection and the timing of the TH appear to be critical in successful trial design. Based on available data, it is apparent that TH and TTM strategies for treating severely injured patients is an important therapeutic consideration that requires more basic and clinical research. Current research involves the evaluation of alternative cooling strategies including pharmacologically-induce hypothermia and the combination of TH or TTM approaches with more selective neuroprotective or reparative treatments. This manuscript summarizes the preclinical and clinical literature emphasizing the importance of brain temperature in modifying secondary injury mechanisms and in improving traumatic outcomes in severely injured patients.

Keywords

Hypothermia; Temperature management; Experimental; Clinical; Secondary injury mechanisms

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Introduction

Traumatic brain injury (TBI) is a serious medical problem in the United States and worldwide. Approximately 1.7 million individuals are evaluated for a TBI each year in the United States with over 257,000 of those individuals hospitalized with 50,000 dying (Corrigan et al., 2010; Langlois et al., 2006). In 2000, it was estimated that TBI produced a \$60 billion cost to society, with over 2% of the population living with some type of long lasting deficit associated with TBI (Faul, 2010; Finkelstein, 2006). Recently, growing emphasis on the detrimental consequences of mild TBI has been appreciated with increased awareness of the high incidence of single and multiple episodes of concussion in both sport related injuries as well as the military. This has led to a greater awareness of the importance of TBI in our society and increased funding for preclinical and clinical studies targeting this serious medical problem (Thurman et al., 1999).

Over the past decades many laboratories have investigated and clarified the pathophysiology of TBI. Various small and large animal models that mimic many of the neuropathological and behavioral consequences of clinical TBI that have been developed. Animal models have clarified the pathophysiological events associated with mild, moderate or severe TBI which are now known to be both complex and progressive in nature (Bramlett and Dietrich, 2014). Based on these findings, specific therapeutic targets have been identified as potentially important to promoting neuroprotection and repair (Radosevich et al., 2013).

Because it is known that TBI is a highly complex injury to the brain, it is no surprise that it has been challenging to identify the pathophysiological mechanisms that are most important to improving outcomes in the clinic (Brain Trauma et al., 2007; Rosomoff and Safar, 1965; Safar, 1988). Indeed, TBI is termed “the most complicated disease of the most complex organ” (Marklund and Hillered, 2011). In this regard, TBI patients can undergo a range of secondary intracranial or extracranial insults that can aggravate the primary traumatic injury process (Chesnut et al., 1993a; Chesnut et al., 1993b; Robertson et al., 1999). For this reason, standard emergency and intensive care protocols are routinely used to inhibit or reduce secondary insults that can aggravate long term outcome.

Preclinical investigations have utilized a variety of clinically relevant TBI models in different species and genders to model brain injury and clarify primary and secondary injury processes that may be targeted by therapeutic interventions (Atkins et al., 2007; Atkins et al., 2010; Bregy et al., 2012; Chatzipanteli et al., 1999; Chatzipanteli et al., 2000; Rosomoff and Holaday, 1954; Wang et al., 2006). Based on preclinical work, it is known that TBI leads to a spectrum of secondary injury mechanisms including ionic fluctuations, excitotoxicity, necrosis and apoptotic cell death and inflammation. Numerous cellular and molecular events have been described that appear to participate in the vulnerability of posttraumatic tissues and the resulting long term functional consequences. Unfortunately, although increased information regarding the pathophysiology of TBI has been obtained and many successful treatments reported in preclinical TBI models, no successful interventions have been translated to the clinic. This short coming may be a consequence of many factors including the relevance of animal models to the clinical situation, therapeutic window limitations or the pharmacokinetic properties of the drugs tested. Also, it has become very clear in recent

years that TBI is a very heterogeneous clinical problem with highly variable pathologies and functional consequences. Thus, it might be difficult for a single treatment strategy that targets a specific injury mechanism in a relatively simple TBI model to work across the broad spectrum of TBI conditions and secondary insults. Indeed, the recent failures of several multicenter trials targeting severe TBI emphasize the difficult task of successfully treating this complex condition.

It is known that small variations in body and brain temperature can play a critical role in patterns of neuronal vulnerability after periods of hypoxia, ischemia or traumatic injury (Busto et al., 1987; Yokobori et al., 2011). Initial observations with transient global ischemia reported that small variations in intra-ischemic brain temperature ranging from only a few degrees played a major role in determining the vulnerability of hippocampal CA1 neurons. While relatively small reductions in temperature significantly protected against ischemic cell damage, mild elevations worsened histopathology and increased mortality. Further, these observations led to the realization that post-injury brain temperature also played an important role in determining the pathological consequences of periods of global and focal ischemia using multiple animal models in several laboratories. Today, therapeutic hypothermia is used to treat several conditions including out-of-hospital cardiac arrest and neonatal hypoxic encephalopathy. Indeed, mild-to-moderate hypothermia is felt to be the most powerful cytoprotective strategy currently known for protecting and promoting long term behavioral improvements in various neurological injury models (Karnatovskaia et al., 2014; Silasi and Colbourne, 2011). In addition, targeted temperature management (TTM) is routinely implemented in most neuro-intensive care units to prevent periods of mild fever that may also represent a clinically relevant secondary injury insult (Rincon et al., 2014; Thompson et al., 2003).

The use of therapeutic hypothermia has also been extensively tested in preclinical models of TBI, subarachnoid hemorrhage and spinal cord injury based on encouraging results with cerebral ischemia and stroke (Dietrich et al., 2009; Dietrich and Bramlett, 2010; Leonov et al., 1990). To date, several clinical trials have been initiated and completed in the area of severe TBI with mixed findings. Interestingly, initial single institutional studies reported beneficial effects with therapeutic hypothermia on controlling elevations in intracranial pressure (ICP) and improving neurological outcomes (Sadaka and Veremakis, 2012; Schreckinger and Marion, 2009; Shiozaki et al., 1993). However, similar to previous attempts to translate encouraging preclinical TBI findings to the clinic, multicenter trials have failed to produce positive effects when large TBI patient populations were recruited. The purpose of this review article is to discuss the TBI field of therapeutic hypothermia and TTM including both preclinical and clinical studies. The article also highlights the failure of therapeutic hypothermia to be successfully translated for multicenter clinical studies, discusses potential reasons for these negative results and future research directions for this evolving research field.

Experimental TBI

Interest in the use of hypothermia and treating brain injury has a long and rich history. Hypothermia therapy is mentioned in ancient Egyptian writings 5,000 years ago and

Hippocrates advised the use of snow and ice packing for states of hemorrhage. Dr. James Curry was one of the first individuals to report the effects of cooling on physiological variables including body temperature, pulse and respiration. Dr. Temple Fay was responsible for reintroducing therapeutic hypothermia to modern day medicine inventing an early cooling blanket (Fay, 1945). Over the years, the beneficial effects of profound hypothermia were emphasized in a variety of experimental clinical conditions following periods of hypoxia, ischemia as well as trauma (Alzaga et al., 2006; Fay, 1945). In the area of brain trauma for example, investigators reported beneficial effects of local hypothermia in small and large animal models of brain injury. In these investigations, the results were regularly confounded by issues associated with the reproducibility of the available animal models and adverse effects of profound extended hypothermia that limited the widespread use of these approaches in the clinic.

As previously mentioned, based on encouraging data from preclinical models of cerebral ischemia several investigations were initiated in established TBI models. Clifton and colleagues first reported that mild hypothermia following a lateral fluid percussion brain injury (FPI) in rats improved motor recovery (Clifton et al., 1991). Subsequent preclinical studies using similar or different TBI models resulting in both focal and diffuse injury also demonstrated that early posttraumatic hypothermia using systemic cooling strategies could in most cases reduce contusion volume and protect against patterns of neuronal vulnerability (Bramlett et al., 1997; Dietrich et al., 1994). In addition, posttraumatic hypothermia also attenuated the severity of diffuse axonal injury (DAI) and altered blood brain barrier (BBB) damage (Bramlett and Dietrich, 2012; Dixon et al., 1998; Kinoshita et al., 2002b; Lotocki et al., 2009; Lyeth et al., 1993; Ma et al., 2009; Smith and Hall, 1996). It should also be mentioned that although most publications reported beneficial effects, some publications emphasized the limitations of restricted periods of mild cooling in models of severe injury or improving more chronic outcomes (Bramlett and Dietrich, 2012).

In addition to reducing histopathological damage, posttraumatic hypothermia consistently improves acute and more chronic behavioral outcome measures including sensorimotor and cognitive function (Bramlett et al., 1995). Posttraumatic hypothermia has also been reported to reduce post-traumatic seizure susceptibilities (Atkins et al., 2010). Importantly, studies also emphasized that mild systemic cooling in several animal models improves clinically relevant outcome measures even when animals were allowed to live months-to-years after the injury (Bramlett et al., 1997; Dietrich and Bramlett, 2010). These findings reported by multiple research groups using different animal models supported the testing of therapeutic hypothermia in the clinic.

An important factor in the successful translation of any neuroprotective intervention to the clinic is the therapeutic window of that particular therapy (Ma et al., 2009). One short coming of many neuroprotective strategies previously advanced to the clinic has been a restrictive treatment window for improving long-term outcomes. In the clinical arena, it may be several hours before a therapeutic intervention can be initiated. In this regard, studies reported that therapeutic hypothermia initiated early but not delayed several hours after TBI produced beneficial effects. For example, in the study by Markgraf and colleagues, early cooling improved outcome whereas a delay of 90 minutes post-injury failed to reduce edema

formation or improve neurological status (Markgraf et al., 2001). In that publication, a relatively restricted duration of hypothermia of 3 hours was tested which may not be optimal for improving long-term outcome.

Another factor that is important in the use of therapeutic hypothermia is the rewarming phase. Povlishock and Wei showed that rapid rewarming after TBI inhibited the beneficial effects of hypothermia on axonal injury and microvascular damage (Povlishock and Wei, 2009). In another relevant study, Matsushita and colleagues tested therapeutic hypothermia using a complicated model of TBI + hypoxia to aggravate traumatic outcome in an attempt to more closely mimic the clinical condition (Matsushita et al., 2001). While hypothermic treatment combined with a slow rewarming phase led to improved protection, rapid rewarming cancelled the beneficial effects of cooling. Rewarming rates are now considered a critical factor when using therapeutic hypothermia in clinical studies.

The fact that therapeutic hypothermia has been shown to be beneficial in multiple models from different laboratories emphasizes the potentially powerful effects of temperature management in TBI. This is an important consideration since in many areas of science, the positive replication of published studies reporting the benefits of neuroprotective agents has been difficult to achieve. Thus, an advantage of hypothermic treatment is that it may target a range of injury mechanisms relevant to the clinical condition, work across multiple animal models and thereby, potentially provide benefits in the heterogeneous TBI population.

Effects of Mild Hyperthermia on TBI

In contrast to the beneficial effects of hypothermia, experimental and clinical studies have emphasized the detrimental effects of mild elevations in core temperature after many types of brain injury (Bao et al., 2014; Dietrich et al., 1996; Dietrich and Bramlett, 2007; Diringer and Neurocritical Care Fever Reduction Trial, 2004; Gaither et al., 2015; Li and Jiang, 2012; Natale et al., 2000; Suzuki et al., 2004). Researchers first noted the detrimental effects of increased hyperthermia in models of cerebral ischemia and stroke showing that both intra-ischemic and post-ischemic temperature elevations aggravated histopathological and behavioral outcomes. In reference to TBI, an induced period of mild hyperthermia (39°C) delayed 1 day after FPI increased mortality and overall contusion volumes (Dietrich et al., 1996). Posttraumatic hyperthermia is also associated with aggravated vascular permeability, edema formation and inflammatory cell infiltrates into injured brain regions when compared to normothermia.

In the clinic, brain injured patients commonly demonstrate periods of apnea (hyperthermia) during the first several days after severe injury (ICU). These periods of hyperthermia can correlate with longer ICU stays and worse outcomes (Kilpatrick et al., 2000; Todd et al., 2009). Also, environmental hyperthermia in prehospital patients with severe TBI is associated with poorer outcomes (Gaither et al., 2015). Similar findings are reported in models of subarachnoid hemorrhage and spinal cord injury where post-traumatic hyperthermia has been shown to increase histopathological injury, edema formation and worsen long term behavioral deficits (Dietrich and Bramlett, 2007; Yu et al., 2001). These studies have led to the hypothesis that TTM strategies that inhibit or limit periods of reactive

hyperthermia may be critical in improving outcomes in severely injured patients. Together, these investigations emphasize the importance of mild elevations in temperature and may indicate the need for temperature management consideration to limit hyperthermia in various clinical conditions.

Mechanisms underlying Temperature Effects

As previously mentioned, the pathophysiology of TBI is multifactorial and involves many injury mechanisms that each may have a significant impact on neuronal dysfunction or cell death. This complexity is a significant factor in determining whether successful treatments can be identified and translated to the clinic. In addition to multiple injury mechanisms, the temporal profile of these injury mechanisms are important as one considers the therapeutic window restrictions for treatment. To address this issue, experimental and clinical investigations have clarified an extensive list of injury processes that are sensitive to brain temperature variations during or following injury (Atkins et al., 2007; Chatzipanteli et al., 1999; Chatzipanteli et al., 2000; Polderman, 2009; Suzuki et al., 2003; Vitarbo et al., 2004). Previous review articles have thoroughly discussed these temperature sensitive processes that include excitotoxicity, free radical generation, programmed cell death and neuroinflammation (Dietrich, 1992; Dietrich et al., 2009; Dietrich and Bramlett, 2010; Han et al., 2015; Li et al., 2015; Lotocki et al., 2011; Truettner et al., 2005; Yenari and Han, 2012; Yenari and Han, 2013). In one early study using in vivo microdialysis, Globus and colleagues for example reported that extracellular levels of glutamate and indicators of free radical formation were dramatically reduced with hypothermia compared to normothermia (Globus et al., 1995). Cellular and molecular approaches have also shown that programmed cell death signaling cascades are affected by hypothermia (Jin et al., 2015). In addition to the established benefits on neuron survival and axonal injury, hypothermia reduces BBB breakdown and improves oligodendrocyte survival after TBI (Jiang et al., 1992; Smith and Hall, 1996). A variety of inflammatory responses to injury including inflammasome activation are also affected by hypothermia with reduced levels of cytokines and chemokines being detected in injured tissues (Chatzipanteli et al., 1999; Chatzipanteli et al., 2000; Kinoshita et al., 2002a; Vitarbo et al., 2004). Hypothermia treatment has been reported to potentiate ERK1/2 activation and downstream signaling components that might underlie the benefits of cooling on cognitive function after TBI (Atkins et al., 2007). In addition to the beneficial effects posttraumatic hypothermia on protection, temperature management strategies may also enhance promote post-traumatic reparative processes like hippocampal neurogenesis, a cellular response associated with improved cognitive recovery after brain injury (Bregy et al., 2012). Taken together, these findings emphasize the beneficial effects of lowering temperature on a wide range of injury or reparative processes that are felt to be important determinants of chronic trauma outcome.

Clinical TBI Studies with Hypothermia

Based on positive preclinical findings, individual institutional clinical studies were initiated to test the benefits of therapeutic hypothermia in severe TBI patients ((POLAR-RCT); Polderman and Andrews, 2011; Suehiro et al., 2015). As previously mentioned, hypothermic treatment was shown in many single institutional studies to consistently improve outcome in

severe TBI patients. For example, Marion and colleagues first reported encouraging findings showing that posttraumatic hypothermia improved patient survival and functional outcome (Marion et al., 1997). Other institutional studies also using relatively small patient numbers showed positive findings including reductions in elevated intracranial pressure.

Unfortunately, although these studies provided encouraging support for a role of hypothermia in the clinic, when this experimental therapy was tested in several multicenter trials, no benefits on neurological outcome were seen in severe TBI patients (Adelson et al., 2013; Beca et al., 2015). Three multicenter studies found either no difference or worse mortality rates in the hypothermia group compared to normothermia (Clifton et al., 2001b; Clifton et al., 2011; Maekawa, 2015; Maekawa et al., 2015). Initially, differences in critical care protocols across recruiting sites that could have confounded the hypothermic treatment effects was reported for the initial National Brain Injury Study Hypothermia (NBISH) (Clifton et al., 2001a). However, a second NBISH also proved negative as well as the Japanese Brain Hypothermia (B-HYPO) trial (Maekawa et al., 2015). Interesting, in the B-HYPO trial, fever control management was reported to significantly reduce TBI-mediated mortality compared to the mild therapeutic hypothermia group (Hifumi et al., 2015). This result is consistent with a recent systematic review indicating that controlled normothermia improved surrogate outcomes of TBI again suggesting a beneficial effect for avoiding fever (Madden and DeVon, 2015).

Several meta-analysis studies have been published based on systemic literature reviews for hypothermic therapy (Crossley et al., 2014; Li and Yang, 2014; Madden and DeVon, 2015; Zhang et al., 2015). Cochrane meta-analysis of all clinical trials of hypothermia for hypothermia have not shown an overall benefit in severe TBI (Marion and Regasa, 2014). In a review by Li and Yan, analysis was conducted on publications listed in PubMed, Medline, Springer, Elsevier Science Direct, Concurrent Library and Google Scholars up to December 2012 (Li and Yang, 2014). The overall estimates reported that hypothermia treatment reduced mortality and unfavorable clinical neurological outcomes. This publication also included stratification subgroup analysis indicating that hypothermia presented a significant reduction of mortality in the Asian population. In a more recent analysis, Crossley and colleagues updated the 2009 results with 20 studies analyzed with 18 providing mortality data (Crossley et al., 2014). In contrast to the previous reviews, evidence was reported to suggest that therapeutic hypothermia might be beneficial although the majority of trials including the single-center trials were of low quality with unclear allocation concealment. However, two large pediatric multicenter clinical trials (Adelson et al., 2013; Beca et al., 2015; Hutchison et al., 2008), also found no significant benefit for therapeutic hypothermia in this patient population (Polderman et al., 2008).

Recently, several hypothermia trials in TBI have been initiated or have ended (Lei et al., 2015; Nichol et al., 2015; Polderman et al., 2002; Polderman, 2004). The European Study of Therapeutic Hypothermia (32–35° C) Trial, an international multicenter randomized control trial examined the effects of titrated therapeutic hypothermia (32–35°C) on ICP and neurological outcome (Andrews et al., 2011; Andrews et al., 2015; Flynn et al., 2015). The results of this trial that enrolled 387 patients at 47 centers in 18 countries has recently been completed and reported that therapeutic hypothermia while successfully reducing

intracranial pressure did not improve functional recovery. Therefore, based on clinical data from several well conducted hypothermia TBI trials, it is clear that a successful translation of preclinical data to the clinic demonstrating the beneficial effects of therapeutic hypothermia on outcome has not been realized.

Possible factors underlying the unsuccessful translational of therapeutic hypothermia treatment for severe TBI patients

The gold standard for translating new therapies to patients with severe TBI is showing efficacy in a Phase III randomized clinical trial testing the therapeutic agent. Disappointing trial results for therapeutic hypothermia have therefore triggered considerable speculation about reasons for the negative outcomes. It should be mentioned that this apparent failure to translate encouraging preclinical data to severe TBI patients using multicenter approaches is certainly not unique to therapeutic hypothermia. Recently, several multicenter trials have failed to demonstrate efficacy with progesterone or erythropoietin, both neuroprotective agents previously reported in preclinical and clinical studies to be effective in targeting severe TBI (Nichol et al., 2015; Robertson et al., 2014; Skolnick et al., 2014; Wright et al., 2014). Thus, one must consider what factors are responsible for the failure of neuroprotective agents to work following severe TBI.

Many investigators have provided multiple opinions on translation failures, specifically targeting TBI. Reasons include the lack of relevant animal models, limitations in the therapeutic window, lack of adequate dose response studies including durations of hypothermia and rewarming protocols (Howard et al., 2015). While no animal model can exactly mimic the human condition, multiple models have been used to evaluate hypothermic effects and to clarify injury mechanisms for protection. It's evident from these experiments that multiple factors may influence the ability of hypothermia to protect including injury severity, when cooling is initiated, the level of hypothermia, the duration of cooling as well as gender. Also, in some recent clinical studies, the potential beneficial effects of therapeutic hypothermia were not directly compared to patients where brain temperature was uncontrolled (Nielsen et al., 2013). Each one of these factors could therefore play a major role in determining whether hypothermia is shown to be beneficial in the clinic.

The complexity of the severe traumatic lesion, may necessitate treatment strategies that are initiated early after injury and maintained for extended durations. This approach could target both acute and more progressive neuronal injury cascades including later elevations in intracranial pressure (ICP). In the recent Eurotherm 3235 TBI trial, targeted therapeutic hypothermia significantly reduce elevated levels of ICP believed to be a major target for neuroprotective strategies. However, the ability to normalize ICP in this trial did not translate to improved behavioral function. This may indicate that ICP in some patients may not be the dominant or only injury mechanism responsible for long-term outcome (Robertson and Ropper, 2015). Alternatively, based on available preclinical data sets, these negative findings might indicate that early cooling is required to reduce the deleterious consequences of multiple secondary injury processes active during the first hours to days after injury. What

may be needed is a clinical study where early cooling is combined with an extended period of hypothermia and where cooling duration is dependent of alterations in ICP or other surrogate biomarkers of progressive injury. It is possible that without the successful targeting of multiple and time sensitive injury processes that the severe degree of evolving damage may override the benefits of a more restricted cooling approach. The Prophylactic Hypothermia Trial to Lessen Brain Injury (POLAR) may provide valuable data to support this hypothesis (Nichol et al., 2015). In addition, the Long-term Mild Hypothermia for severe traumatic brain injury (LTH-1) trial will test whether hypothermia for 5 days is beneficial (Lei et al., 2015).

There is also a discussion that functional outcome measures that are normally used in clinical trials may not be sensitive enough to differentiate between the potential benefits of a particular therapy. It is therefore important that more work be done before translating therapeutic interventions to large phase III multicenter trials. Thus, it may be important to increase the frequency of phase II trials to maximize chances of successful translation into the general population (Chase, 2015).

The heterogeneity of TBI patients is another factor that is commonly discussed that could have a major impact on the beneficial effects of hypothermic therapy. The beneficial effects of hypothermia treatment are known to vary between injury models depending on differences in severity or neuropathological characteristics (i.e., focal vs diffuse). Thus, it may be very difficult for a single therapy to successfully treat the wide range of different types of traumatic insults. Interestingly, Clifton and colleagues introduced new findings from a post-hoc analysis of the NABIS: H multicenter trials indicating that the beneficial effects of therapeutic hypothermia may be selective to a specific patient population (Clifton et al., 2011). The evaluation of this data set indicated that while early hypothermia improved outcomes in patients undergoing surgical decompression surgery for focal insults, early cooling did not improve outcome in patients with diffuse brain injury. In that analysis, precooling prior to decompression surgery appeared to have the most dramatic beneficial effects in the decompression surgery group compared to normothermia. These observations may indicate that early cooling prior to decompression surgery may benefit patient outcomes by reducing the detrimental effects of reperfusion injury that can occur after cortical decompression.

Many TBI research programs emphasize the bench-to-bed philosophy of moving new treatments to the clinic. However, especially with failures, it may also be important to consider taking clinical data back to the laboratory to clarify scientific questions and to test new hypotheses. Based on Clifton's clinical observations, animal experiments were initiated using a preclinical rodent model of surgical decompression to evaluate whether such a proposed pre-cooling strategy would be beneficial in a severe TBI model. Indeed, studies reported by Yokobori and colleagues showed that mild hypothermia introduced prior to decompression surgery produced the best protection and improved biomarker indicators of tissue damage (Yokobori et al., 2013a; Yokobori et al., 2013b). These findings support the general concept that specific therapeutic approaches may be most appropriate for selective types of severe TBI. The Hypothermia for Patients requiring Evacuation of Subdural Hematoma (HOPES) trial is currently recruiting patients to test this hypothesis in TBI

patients that undergo decompression surgery including several centers in the United States, Japan and China.

Future Directions and Conclusions

The field of therapeutic hypothermia has a long and rich history including both successes and failures (Marion and Bullock, 2009; Marion and Regasa, 2014; Newmyer et al., 2015). In the late 1980's there was a dramatic resurgence of hypothermic research when it was discovered that relatively mild reductions in temperature could dramatically protect the brain from injury. In addition, the importance of mild elevations in temperature as a clinically relevant secondary insult was also appreciated. These observations led to an increase in basic, translational and clinical investigations assessing the beneficial effects of hypothermia and the translation of therapeutic hypothermia to the clinic as a powerful cytoprotective strategy. In parallel, researchers evaluated pathophysiological mechanisms shown to be sensitive to mild variations in temperature. Small temperature changes were shown to be beneficial by targeting multiple injury mechanisms in contrast to a single therapeutic target. This multi-target characteristic of therapeutic hypothermia appears most advantageous for the treatment of severe TBI with temperature monitoring and maintenance routinely used as a strategy to improve outcomes in injury models and in some clinical conditions. Future studies will continue to evaluate the cellular and molecular mechanisms underlying the effects of hypothermia and clarify what specific patient populations may benefit best from therapeutic hypothermia therapy. Also, the continued testing of new methods to induce hypothermia including pharmacologically-induced hypothermia or the testing of selective brain hypothermia protocols could also help advance this therapy (Gu et al., 2015).

It may be also important to combine therapeutic hypothermia with more target directed pharmacological agents in a particular patient population. It is already appreciated that hypothermia combined with specific neuroprotective drugs may have additive or synergistic effects. If synergistic effects are established with clinically relevant compounds, the combination with therapeutic hypothermia or controlled temperature management may indeed be an important strategy for future clinical investigations.

Another important future need includes the identification of specific biomarker strategies that can help determine injury severity and assess the treatment effects of therapeutic hypothermia (Lei et al., 2015). The achievement of this goal would be most helpful as therapeutic hypothermia is directed toward more selective patient populations to reduce patient heterogeneity experienced in previous multicenter hypothermia trials. Specialized or precision medicine is now demanding that treatments be more individualized to produce maximum benefits. The use of circulating biomarkers or other noninvasive strategies as indicators of treatment related protection may be something that will help move this experimental therapy forward.

Finally, we need to learn from the clinical trial failures and take this information back to preclinical models as we investigate new injury mechanisms and targets for protection. Although discouraging, the use of hypothermia as a clinical treatment as well as experimental tool has helped advance the field of acute CNS injury and repair. Continued

work in parallel with preclinical and clinical research should allow investigators to address new hypothesis to better understand this extremely important clinical program and develop and test new therapeutic interventions.

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Highlights

- Preclinical/clinical studies have assessed the efficacy of therapeutic hypothermia
- Induced elevations in temperature posttrauma heighten secondary injury mechanisms
- The use of TH and TTM for treating TBI continues to evolve
- Failed multi-center clinical trials in severe TBI are discussed