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# **Hypothermia for Intracerebral Hemorrhage, Subarachnoid Hemorrhage & Spinal Cord Injury**

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David E. Tannehill

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## **1. Introduction**

As described previously in this book, hypothermia likely has many positive effects on injured brain and spinal cord to limit the damage caused by secondary injury. This secondary injury has multiple mechanisms, including inflammation, excitotoxicity, calcium homeostasis, blood brain barrier damage, release of toxic intermediates including free radicals, as well as cell necrosis & apoptosis (1). Hypothermia has been shown to be an effective treatment for comatose survivors of out of hospital cardiac arrest to both improve mortality and neurologic outcomes (2, 3). Much less is known about the role of hypothermia for treating patients that have suffered an intracerebral or subarachnoid hemorrhage. Experience and literature on the subject is quite limited. The same is true for hypothermia in the treatment of acute spinal cord injury. In fact, data on this topic is even more limited.

However, in the coming years it is likely that we will see more research on this important topic. The technology available to clinicians for achieving the treatment goals of this strategy has rapidly expanded in the past decade. Additionally, its ease of use and increasing familiarity amongst clinicians and intensive care unit staff will only help in growing the field. The basic science background, while not extensive, is at least encouraging and it is expanding. The clinical use, or at least consideration of this therapy is slowly beginning to expand as well. Options for medical therapy to improve outcomes in ICH, SAH & SCI are limited. Hopefully this continued work will improve upon that. This chapter will explore what has been published on these topics to this point.

## **2. Therapeutic hypothermia for acute spinal cord injury**

In the 1960's and 1970's, multiple investigators published data examining the possibility of employing hypothermic therapy to improve outcomes in acute spinal cord injury. At that time, most of the studies focused on local cooling via the administration of cold saline to the

spinal cord during decompressive laminectomy and durotomy (4-6). However, these studies were not rigorous randomized controlled trials and were fraught with multiple confounders, such as the concomitant administration of corticosteroids and the potential effects of surgery itself (7,8). This, combined with the technical difficulty and invasive nature of local cooling, lead to the general abandonment of the idea.

As technology improved and our understanding of the possible beneficial effects of systemic hypothermia grew, so did interest in applying this strategy to the acute spinal cord injury patient (9,10). Multiple animal studies have suggested a positive effect of either locally or systemically applied therapeutic hypothermia (9). However, clinical experience in the modern era is minimal. In 2010, there was a high-profile case of an NFL football player suspected to have a spinal cord injury who was treated with systemic hypothermia (11). This case garnered the attention of the mass media in addition to the medical community. However, it is important to recognize that it is impossible to discern if this patient's excellent outcome can be in any way attributed to therapeutic hypothermia. That case does add to the literature describing the safe use of targeted temperature therapy in acute spinal cord injury. The largest and most often quoted case series for therapeutic hypothermia in this patient population is a retrospective review described by Levi et al in 2009 (12). This group describes their institutional experience with therapeutic hypothermia in 14 adult patients with acute, complete cervical spinal cord injury who presented to their institution over a two year period. Only complete cervical spinal cord injury patients with a GCS 15 were considered for their hypothermia treatment protocol. An intravascular cooling device was used to achieve and maintain a core body temperature of 33°C over a 48 hour period. Corticosteroids were not used. All patients underwent surgical intervention. Patients were then rewarmed over a 24-32hr period. This group of patients averaged 39.4 years old from a range of 16-62years. Induction of hypothermia began within 9.17 $\pm$ 2.24hr and time to target temperature was 2.72 $\pm$ 0.42hr. They documented a strong correlation between temperature and heart rate. Additionally, in one patient, CSF temperature was measured and found to closely approximate core temperature. Importantly, none of the 14 patients suffered a life-threatening adverse event attributable to therapeutic hypothermia. The adverse events described were primarily respiratory and closely approximated the type and rate of adverse events experienced in an historical control cohort. In a follow-up manuscript, Levi et al describe the clinical outcomes of this patient cohort (13). All 14 patients were American Spinal Injury Association and International Medical Society of Paraplegia Impairment Scale (AIS) A on admission. 8/14 patients remained so, but 3 improved to B, 2 to C and one patient had dramatic improvement to AIS D. Importantly, none of the patients worsened. A control group of patients only had 3/14 patients improve AIS grade compared with the six in the hypothermia group, a non-statistically significant difference. While the low number of patients, strict inclusion criteria, observational nature of study and use of an historical control may temper enthusiasm for these results, they are nonetheless intriguing and provide an excellent basis for developing future studies.

As mentioned previously, medical therapies for acute spinal cord injury are extremely limited. However, with future study, perhaps therapeutic hypothermia's role in treating the 11,000-12,000 spinal cord injury patients per year in the United States can further be defined (14).

### 3. Therapeutic hypothermia for intracerebral hemorrhage

Intracerebral hemorrhage (ICH) accounts for approximately 10% of all cerebral vascular accidents in the United States and carries a mortality rate of up to 50% (15,16). Options for medical therapy are extremely limited and are primarily focused on supportive therapy (17). Mayer et al investigated the potential use of rFVIIa for improving outcome and established that this therapy may in fact improve hematoma volume, but its impact on outcomes was limited (18). Hematoma volume & growth does correlate with various outcome measures (19-21), but so does perihemorrhagic edema (22-25). ICH is associated with secondary injury characteristics that are similar to ischemia and ischemia-reperfusion, including blood-brain barrier disruption, inflammation and edema. The edema progresses through three phases related initially to hydrostatic forces & clot retraction, then activation of the coagulation cascade and thrombin formation and later, via RBC lysis and hemoglobin-induced neuronal toxicity (26). This edema – termed *perihemorrhagic edema* – has been associated with poor outcomes (22, 23, 25). Data from animal models of ICH suggest that hypothermia can improve these injurious processes, but not outcomes (27-33).

There is a suggestion that the application of therapeutic hypothermia may be beneficial in preventing the progression of perihemorrhagic edema and improving outcomes in patients who suffer intracranial hemorrhage (34). In a pilot study by Kollmar et al, hypothermia was determined to be safe as well as potentially provide a positive effect on ICH perihemorrhagic edema (25). This was a comparison of 12 patients w/ supratentorial ICH >25mL in volume cooled with an intravascular cooling device to 33 degrees C with 12 historical controls. Amongst the control cohort, there were more patients with uncontrolled intracranial hypertension, perihemorrhagic edema progression and death. In a followup study by the same group, Staykov et al described similar findings with 25 patients with large ICH as compared with an historical control group (35). Again, perihemorrhagic edema remained mostly unchanged in the hypothermia group, but steadily increased in the historical control group, with a statistically significant difference in perihemorrhagic edema volume. This difference was also associated with a suggestion of mortality difference, but with such a small sample size it was not statistically significant. The mortality rate was 8.3% in the hypothermia cohort, 16.7% in the control group at 3 months and 28% vs 44% at one year. There is a prospective, multicenter, randomized controlled phase II trial currently underway to more formally evaluate this question using a similar protocol (36).

### 4. Therapeutic Hypothermia for Subarachnoid Hemorrhage

As in all neurocritical care related illnesses, fever control may be important for minimizing secondary injury (37). In subarachnoid hemorrhage, this is particularly true. As many as 72% of all SAH patients may experience fever (38). Infection should always be ruled out and treated aggressively (39); however, the fever needs to be controlled whether it is secondary to infection or not. Fever in SAH is strongly linked to poor outcome and increased length of stay (40), as well as vasospasm (41, 42), ischemic injury (43), cerebral edema and worsened intracranial hypertension (44). Even a single episode of fever has been associated with

poorer outcomes. However, one can only definitively say that fever is *associated* with worsened outcomes, it may not be *causative*. In other words, it may simply be a marker of bad outcomes (45).

Whether fever is simply a marker for bad outcomes or something more, there is a suggestion that controlling fever may actually be neuroprotective. Oddo et al demonstrated that induced normothermia in 18 SAH patients resulted in a lower lactate-pyruvate ratio, fewer metabolic crises and lower ICP (46). But what about therapeutic hypothermia as a primary treatment modality – not just for fever control? Mild hypothermia has been shown to decrease cytotoxic edema, lactate accumulation and improve the metabolic stress response to SAH in rats (47). It has also been shown to lower ICP and improve outcomes in rats, including decreased neurologic deficits (48). In a dog model of SAH, therapeutic hypothermia decreased cerebral vasospasm, possibly by decreasing the rise in endothelin-1 and lessening the decrease of NO in CSF and the blood (49). In patients with SAH treated with therapeutic hypothermia, Kawamura used PET scans to demonstrate that hypothermia did decrease cerebral blood flow and oxygen metabolic rate (50). Seule et al. treated 100 patients with SAH who developed intracranial hypertension, symptomatic cerebral vasospasm or both, with mild therapeutic hypothermia (51). The majority of these patients had poor-grade SAH. 90 patients were evaluated at follow-up, 32 (35.6%) had survived with good neurologic outcome (Glasgow Outcome Scale 4 or 5) and 43 (47.8%) died. Side effects were common, including electrolyte disorders, pneumonia, thrombocytopenia and septic shock. From this study, the authors conclude that therapeutic hypothermia is a viable “last-resort option”, but side effects are common and potentially severe.

One of those common side effects of this therapy, shivering, can be detrimental to patients. Similar to any condition for which therapeutic hypothermia is employed, shivering should be avoided if possible and treated aggressively if present. Shivering has been associated with higher oxygen consumption, reduced PbtO<sub>2</sub>, higher ICP and lower CPP and higher resting energy expenditure (52-54). A substudy of the Intraoperative Hypothermia Aneurysm Surgery Trial revealed that bradycardia, a common and expected side effect of hypothermia, was associated with a higher 3-month mortality rate after SAH. “Relative tachycardia” and nonspecific ST-T wave changes, also common with hypothermia therapy, were also associated with a mortality difference. The implications of these findings are not clear, but should be kept in mind when using this therapeutic approach (55).

## 5. Conclusion

Therapeutic hypothermia has already been shown to have a positive impact on survival and neurologic outcome for survivors of out-of-hospital cardiac arrest (2, 3). That benefit likely is related to hypothermia’s impact on the multiple mechanisms of secondary brain injury. There is certainly potential for therapeutic hypothermia to reduce the secondary injury that results from brain and spinal cord injury as well. Many animal studies, but to this point only limited clinical studies, have suggested such an effect in treating patients that have suffered spinal cord injury, intracerebral hemorrhage or subarachnoid hemorrhage. Fortunately, the



technology available to help us achieve and maintain the goals of targeted temperature management has made it easier to do so. The availability of that technology and increasing familiarity with its use will only serve to help investigators understand the potential impact of this therapy in brain and spinal cord injury. Medical therapy for these conditions is limited. Hopefully, future studies will clarify the potential role of therapeutic hypothermia in improving outcomes for these potentially devastating conditions.

## Author details

David E. Tannehill

*Department of Critical Care Medicine, Mercy Hospital, St. Louis, USA*

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