Prolonged Mild-to-Moderate Hypothermia for Refractory Intracranial Hypertension

Abstract

Background: Therapeutic hypothermia is an emerging therapy for brain injury and cerebral edema. Hypothermia is known to reduce death and neurologic morbidity in survivors of cardiac arrest from ventricular fibrillation. Traumatic brain injury (TBI) trials studies of short-term hypothermia (24 to 48hours) have had conflicting results. Recent evidence however suggests prolonged hypothermia (48 hours to 14 days) may be beneficial for TBI and select cases of nontraumatic brain injury especially when the duration of cerebral edema and intracranial hypertension is expected to last longer than 24 hours.

Case Report: A 43-year-old female presented with a Fisher grade 4 aneurysmal (anterior communicating artery) subarachnoid hemorrhage. The patient was comatose upon transfer to our hospital, was intubated, and had immediate aneurysm coiling. The patient had a right external ventricular drain (EVD) placed for acute hydrocephalus and intracranial pressure (ICP) monitoring. The patient developed severe vasospasm of several intracranial vessels requiring angioplasty on two consecutive days, and hypertensive, hypervolemic, hemodilution therapy (HHH). On the ninth day, ICP went above 20mmHg and computed tomography (CT) showed global cerebral edema. For the next 17 days, the patient had refractory intracranial hypertension, requiring sedation, neuromuscular blockade, hyperosmolar therapy (3% infusion, and 23.4% saline boluses), thiopental coma with burst suppression, and hypothermia (31 to 34C). Hypothermia continued for a total of 14 days before ICP and edema on CT normalized.

Conclusion: We report the first case of prolonged therapeutic hypothermia over a total of 14days to control nontraumatic brain injury-related refractory intracranial pressure and global cerebral edema. More studies are needed comparing clinical outcomes and complication rates between short duration and prolonged hypothermia for brain injury.

Keywords: Intracranial hypertension, hypothermia, subarachnoid hemorrhage

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Hypothermia has been shown to have neuroprotective benefit after cardiac arrest associated with ventricular fibrillation.[1,2] However, hypothermia's role remains unclear for other forms of brain injury, including ischemic stroke, traumatic brain injury (TBI), and raised (ICP).[2-9] We report the benefit of mild to moderate (31-34C) hypothermia, over 14 days, for controlling refractory intracranial hypertension, following severe, nontraumatic brain edema after subarachnoid hemorrhage (SAH).

Case Report

A 43-year-old woman presented with acute headache and had a Fisher grade 4 aneurysmal (anterior communicating artery) SAH. After transfer to our hospital, she progressed rapidly to coma (Glasgow Coma Scale- E1M5V1T) and had immediate aneurysm coiling. The patient was intubated for respiratory failure, and had a right external ventricular drain (EVD) placed for acute hydrocephalus and ICP monitoring. This drain subsequently failed and was replaced with an EVD on the left side. On the fourth day, severe vasospasm of the left middle cerebral artery (MCA) and bilateral anterior cerebral arteries (ACA) required angioplasty of the left MCA and ACA, and hypertensive, hypervolemic, hemodilution therapy (HHH). The patient required angioplasty of the right MCA and ACA on the subsequent day, due to severe vasospasm. On the ninth day, ICP went above 20mmHg; her right pupil became dilated, and computed tomography (CT) showed global cerebral edema (Figure 1). CT Perfusion showed global hyperemia (not shown).

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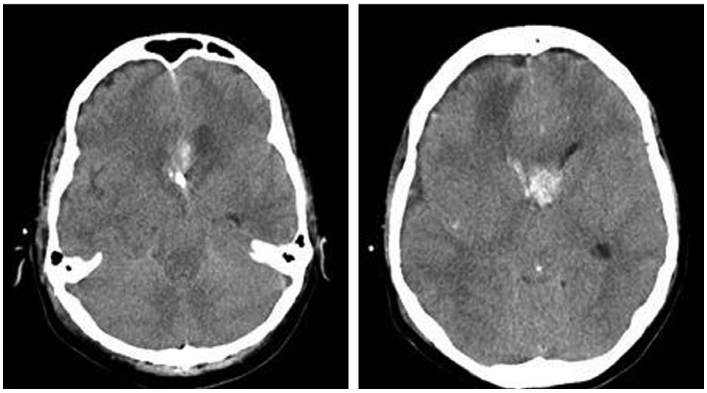

Figure 1. Non-contrast Head CT showing global cerebral edema, SAH, IVH, and EVD

For the next 17 days (Figures 2 and 3), the patient had refractory intracranial hypertension, requiring sedation, neuromuscular blockade, hyperosmolar therapy (3% infusion, and 23.4% saline boluses), thiopental coma with burst suppression, and hypothermia (31 to 34C). Hypothermia continued for a total of 14 days before ICP (Figure 3) and edema on CT (Figure 4) normalized. The patient's EVD was removed, but she required tracheostomy and percutaneous gastrostomy (PEG). No significant hemodynamic issues or arrhythmias were observed. The patient was discharged to a rehabilitation facility and returned to clinic three months after having her tracheostomy and PEG removed. The patient returned to her normal activities of daily living.

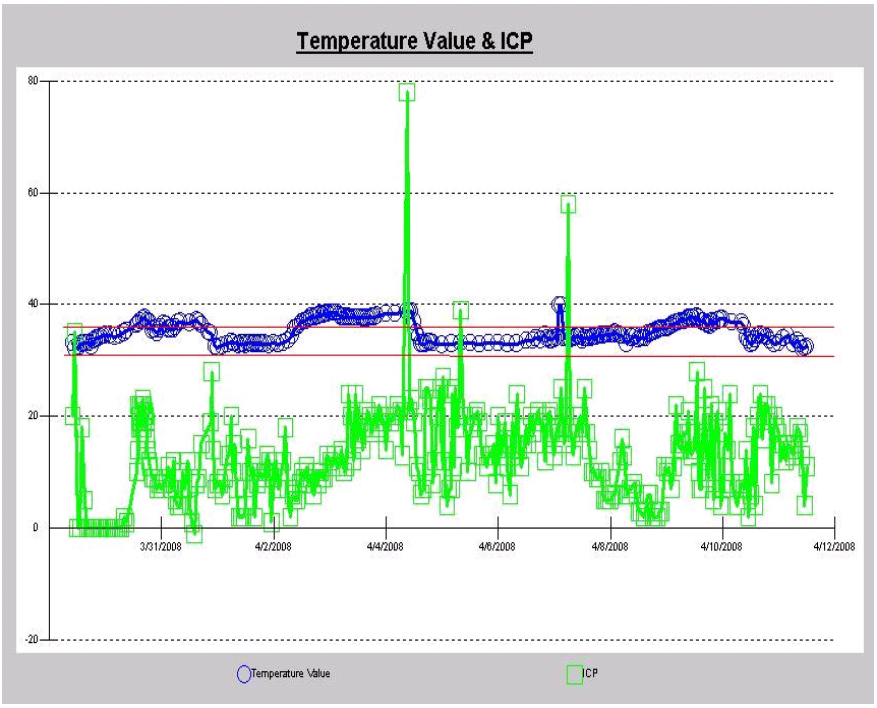

Figure 2. Graph of Prolonged Hypothermia - Core temperature (blue) in Centigrade (C) and ICP (green). Start date of hypothermia 3/28/08 2100hrs (32.8C), with intermittent attempts at raising temperature to normothermic range with resultant spikes in ICP requiring re-induction of hypothermia to control ICP. Upper Red Line 34C, lower red line 32 C.

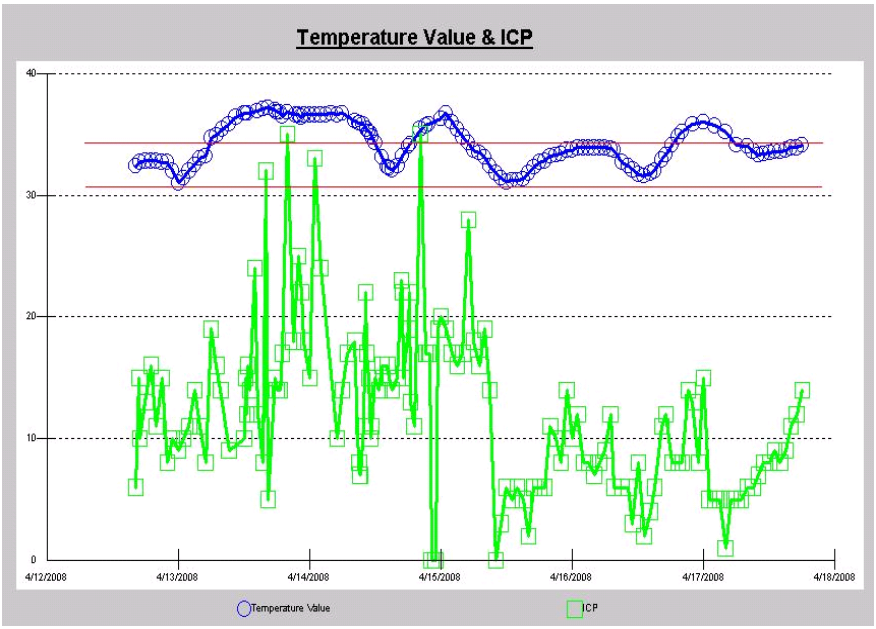

Figure 3. Graph of Prolonged Hypothermia (continued) – Core Temperature (blue) and ICP (green) from 4/12/08 until the end date of hypothermia 4/17/08 1800hrs (Temp – 34.1C). Upper Red Line 34C, lower red line 32 C. Multiple attempts were made at normalizing temperature via slow rewarming (with multiple spikes in ICP) requiring repeat hypothermia until resolution. 3/28/08 to 4/17/08 spans 17 days but 6 days had core temperature above hypothermic (31-34) range. Thus, total time hypothermic =14days.

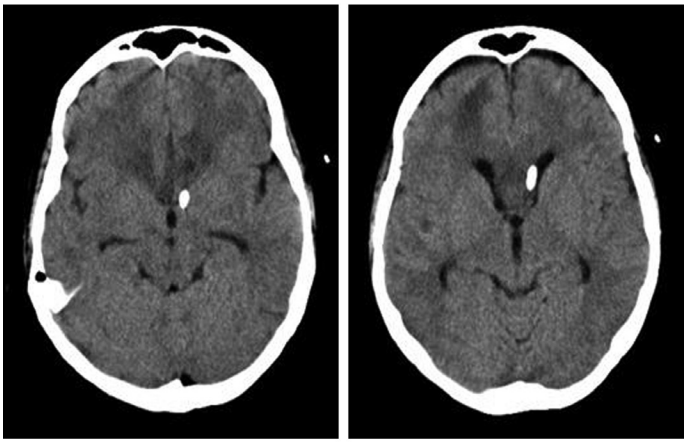

Figure 4. Non-contrast Head CT. CT 17 days later showing resolving global cerebral edema and left frontal EVD with bifrontal white matter changes from EVD placement.

Discussion

Short-term hypothermia (24-48 hours) is neuroprotective in cardiac arrest survivors, with witnessed ventricular fibrillation/tachycardia.[1,2] However, short-term hypothermia's benefit remains controversial in TBI, despite the publication of more than 30 studies.[3, 5-7, 9-12] The controversy may be due to various forms of brain injury and cerebral edema that develops after the initial 24-48 hours.

There are few reports of prolonged or long-term hypothermia (48 hours to 14 days) compared to short-term hypothermia (less than 48 hours) within the TBI literature.[11, 13, 14] These reports seem to indicate benefit for prolonged hypothermia compared to shorter duration hypothermia.[11, 14] Hypothermia has multiple neuroprotective effects, including reducing cerebral blood flow/cerebral metabolic rate of oxygen (CMRO2), suppressing neuronal and glial excitotoxicity/cell death cascades, and reducing expression of aquaporin 4[15, 16] leading to cerebral edema.

Few studies compare short-term and long-term hypothermia.[11, 17, 18] The largest study by Jiang et al reported 108 cases with long-term hypothermia compared to 107 cases in short-term hypothermia.[11] The authors reported 47 cases (43.5%) had favorable outcome in the long-term mild hypothermia group at six months, compared to 31 cases (29.0%) with favorable outcome

Table 1: Physiologic Relevance and Complications of Hypothermia[19-30]

Physiologic Response	Physiologic Impact	Management
Shivering[19, 21, 23]	Increases BMR and CMRO2	Increase sedation, neuromuscular blockade, Demerol, buspirone, dexmedetomidine, intravenous magnesium[30]
Cardiac arrhythmias[1, 2, 21, 26]	Bradycardia, J (Osborn) waves, prolonged PR, QRS, and QT intervals, and atrial arrhythmias.	ECG monitoring, tight control of hypothermia within 32-34C range, electrolyte management, discontinuation of hypothermia as last resort
Hemodynamic Reduced cardiac index, increased SVR[1]	Hypotension	Intravenous fluids, vasopressor agents as needed, optimize core temperature
Diuresis[22]	Intravascular volume depletion, hypophosphatemia,[27] hypokalemia, hypomagnesemia, and hypocalcemia	Intravenous fluids, check electrolytes frequently and replace as needed
Decreased insulin secretion and insulin sensitivity	Hyperglycemia[9, 22]	Frequent glucose checks and insulin drip
Depressed immune function[28]	Infection rates	Central line and ventilator 'bundles' preventing bacteremia and ventilator-associated pneumonia, daily sedation cessation, proper oral care in comatose, ventilated patients
Mild coagulopathy[24]	Increased heparin effect[24]	Rule out/manage DIC, adjust intravenous heparin rates if applicable
Vasoconstriction (skin, visceral, and coronary)[19, 21, 22]	Skin integrity loss (cold thermal injury), limb cyanosis, coronary ischemia	Frequent nursing checks of skin integrity and limb perfusion, serial ECG during hypothermia, extremity warming (boots, blankets) for limbs, raise core temperature as needed
Reduced drug clearance (up to 30% at 34C)[29]	Prolonged sedation	Adjust sedatives and NMB infusions

Abbreviations used: BMR – basal metabolic rate; CMRO2 – cerebral metabolic rate of oxygen; SVR- systemic vascular resistance; DIC –disseminated vascular coagulation; NMB – neuromuscular blockade.

in the short-term mild hypothermia group ($P < 0.05$). Intracranial pressure rebounded upwards after rewarming in the short-term mild hypothermia group but not in the long-term mild hypothermia group ($P < 0.05$). In terms of complications, there was no significant difference in the incidence of stress ulcer, epilepsy, pulmonary infection, or intracranial infection between the two groups.

In a meta-analysis of 12 randomized trials of hypothermia for TBI, McIntyre et al[9] report that hypothermia longer than 48 hours in TBI patients was more effective than short-term hypothermia in reducing the risk of death or poor neurologic outcome (relative risk [RR], 0.70; 95% CI, 0.56-0.87 and RR, 0.65; 95% CI, 0.48-0.89, respectively) compared to normothermia. This data is also consistent with animal data suggesting that TBI triggers a cascade of events in which cerebral edema lasts longer than 24-48 hours, often four or even seven days.[12] Therefore, cooling for longer than 48 hours in select TBI cases may be required to derive the maximal clinical benefit compared to shorter duration hypothermia. Prolonged hypothermia also appears to benefit other forms of non-traumatic global cerebral edema, such as our case in controlling refractory ICP from global cerebral edema. Our case developed global cerebral edema from lost autoregulation and hyperemia during 'HHH' therapy after balloon angioplasty of intracranial vessels for severe vasospasm after SAH. Further studies are needed comparing prolonged vs short term hypothermia on clinical outcomes and complications of hypothermia.

Complications can occur with hypothermia, and are shown in Table 1. The mostly common physiologic response to hypothermia is shivering. Shivering represents a formidable autonomic reflex that requires a combination of measures (Table 1) to control.[19, 20] Arrhythmias occur in hypothermia, most commonly bradycardia,[21, 22] with temperatures lower than 33 C. There were no statistically significant differences in pneumonia, bleeding of any severity, sepsis, pancreatitis, renal failure, hemodialysis, pulmonary edema, seizures, or lethal or prolonged arrhythmias in the European cardiac arrest study using 32 to 34 C mild hypothermia.[2] Pancreatitis (amylase elevation) was reported in one TBI hypothermia study but used moderate hypothermia (i.e., temperature below 32 to 33 C).[23] We did not observe any major complications in our case. We did observe a mild elevation in the activated partial thromboplastin time (aPTT) (38 to 60 range, normal 23 to 36) during deep vein thrombosis prevention dose of subcutaneous heparin (5000 units every 8 hours) near the end of the 14-day period of hypothermia. The heparin was held for a day and the aPTT normalized. Increased heparin effect has also been reported elsewhere although primarily with intravenous heparin.[24] No bleeding complications occurred.

Conclusion

We report the first case of prolonged therapeutic hypothermia over a total of 14 days to control nontraumatic brain injury-related refractory intracranial pressure and global cerebral edema. While more than 30 trials have studied TBI and short-term hypothermia with conflicting results, prolonged hypothermia may be beneficial for TBI and select cases of non-traumatic brain injury especially when the duration of cerebral edema and intracranial hypertension is expected to last longer than 24 hours. More studies are needed comparing clinical outcomes and complication rates between short duration and prolonged hypothermia for brain injury.

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