Prolonged Hypothermia as a Bridge to Recovery for Cerebral Edema and Intracranial Hypertension Associated with Fulminant Hepatic Failure

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Abstract

Background To review evidence-based treatment options in patients with cerebral edema complicating fulminant hepatic failure (FHF) and discuss the potential applications of hypothermia.

Method Case-based observations from a medical intensive care unit (MICU) in a tertiary care facility in a 27-year-old female with FHF from acetaminophen and resultant cerebral edema.

Results Our patient was admitted to the MICU after being found unresponsive with presumed toxicity from acetaminophen which was ingested over a 2-day period. The patient had depressed of mental status lasting at least 24 h prior to admission. Initial evaluation confirmed FHF from acetaminophen and cerebral edema. The patient was treated with hyperosmolar therapy, hyperventilation, sedation, and chemical paralysis. Her intracranial pressure remained elevated despite maximal medical therapy. We then initiated therapeutic hypothermia which was continued for 5 days. At re-warming, patient had resolution of her cerebral edema and intracranial hypertension. At discharge, she had complete recovery of neurological and hepatic functions.

Conclusion In patients with FHF and cerebral edema from acetaminophen overdose, prolonged therapeutic hypothermia could potentially be used as a life saving therapy and a bridge to hepatic and neurological recovery. A clinical trial of hypothermia in patients with this condition is warranted.

Introduction

A 27-year-old Caucasian female was admitted to the medical intensive care unit (MICU) from an outside hospital with fulminant hepatic failure (FHF) secondary to acetaminophen overdose. On initial presentation to the outside emergency room, the patient was noted to be lethargic, though still following simple commands. Her vitals at initial presentation were blood pressure of 128/77 mmHg, pulse rate of 130, respiratory rate of 20, temperature of 97°F, and Glasgow coma scale (GCS) of 12 (E3, V3, M6). The initial acetaminophen level was 99 mg/dl and blood glucose was 66 mg/dl for which 25 g of iv dextrose was given (50 ml of 50% dextrose). Blood glucose improved to 186 mg/dl. The patient was started on intravenous *N*-acetyl cysteine (NAC), given vitamin K intravenously and was transferred to our MICU. There was no history of alcohol, illicit drugs, or other potentially hepatotoxic drug use.

On admission to our ICU 7 h after initial presentation, the patient was found to have Grade 3 encephalopathy (West Haven Classification system [1] Grade 3 encephalopathy-Somnolent but can be aroused, unable to perform mental tasks, disorientation about time and place, marked confusion, amnesia, incomprehensible speech). She had a heart rate of 120, BP of 136/60 mmHg, temperature of 102°F, respiratory rate of 24, 6 mm bilateral pupils reacting briskly to light, and no meningeal signs. Her GCS declined to 6 (E1, V2, M3). Cardiac, respiratory, and abdominal exams were otherwise unremarkable. There were no clinical signs

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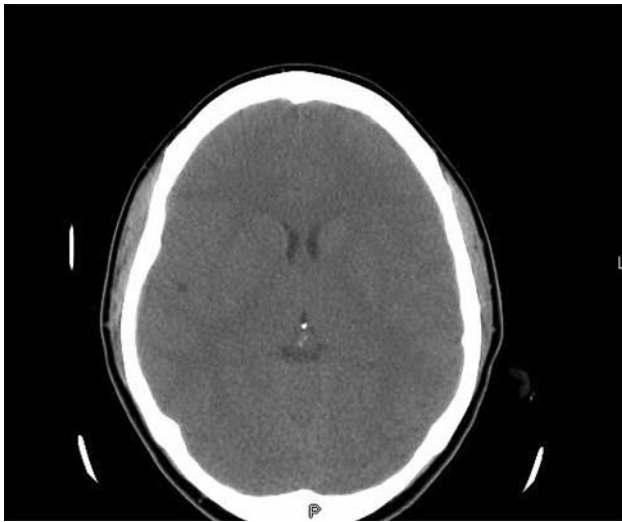e-mail: rnanchal@mcw.edu

Fig. 1 CT scan of brain on admission showing cerebral edema

of herniation. The patient was intubated for airway protection. A CT scan of the head demonstrated diffuse cerebral edema (Fig. 1). She was diagnosed with FHF complicated by cerebral edema secondary to acetaminophen toxicity. Emergency orthotropic liver transplantation workup was initiated.

A right sided Camino Parenchymal intracranial pressure (ICP) Monitoring Catheter (Camino, Camino Laboratories, San Diego, USA) was placed for continuous ICP monitoring after correction of her coagulopathy with 7000 μg of recombinant Factor VIIa (Novoseven, 80 mcg/kg) and 10 units of cryoprecipitate (INR improved from 3.4 to 1). Her initial ICP was 35 mmHg (normal less than 18 mmHg). Initial medical therapy of raised ICP included elevation of the head of the bed to 30°, hyperventilation, sedation with propofol and fentanyl, chemical paralysis for ventilator synchrony and administration of hyperosmolar therapy in the form of mannitol and hypertonic saline. Lactulose, metronidazole, and continuous renal replacement therapy (CVVH) were started in an effort to lower ammonia levels (ammonia level on presentation was 535 mmol/l). Propofol dose was titrated up to 60 mcg/kg/h, serum sodium went up to 156 meq/dl after hypertonic saline therapy and she received one dose of intravenous mannitol (50 g). Her ICP remained refractory to maximal medical therapy and continued to demonstrate spikes up to 60 mmHg. Barbiturate coma was considered but we elected not to use this therapy because of the patient's need for hemodynamic support and FHF. Therapeutic hypothermia initiated at this time with icepacks, as well as surface cooling device (Blanketrol II Hypothermia Unit, Cincinnati Sub-zero, Cincinnati, USA). Core body temperature was monitored using Foley catheter temperature probe (Foley temperature probe, Smiths Medical, IN, USA). Her core body temperature was lowered to 91°F. The rate of desired

cooling was 1–1.5°F/h to achieve target temperature within 6 h; however, the patient cooled more rapidly than expected and was at target temperature within 2 h. This improved her ICPs which decreased over the 2-h period to 14–16 mmHg (Fig. 2). Therapies including sedation, analgesia, paralysis, and hypertonic saline were continued to control her ICP. Other treatments continued were broad spectrum antibiotics, close blood glucose monitoring, and NAC for the acute liver failure. Plasma sodium concentrations were maintained between 150 and 155 meq/l. Norepinephrine intravenous infusion was used to maintain mean arterial blood pressure to keep the cerebral perfusion pressure above 60 mmHg. Twenty-four hours after the initiation of therapeutic hypothermia her ICP remained stable and liver functions as well as coagulopathy began to improve. The patient remained sensitive to small changes in core temperature. A head CT scan done on day 3 demonstrated worsening of cerebral edema (Fig. 3).

Therapeutic hypothermia was continued over the next 48 h. Midazolam, propofol, and fentanyl were continued for sedation and analgesia. Lactulose, metronidazole, and CVVH were continued to lower ammonia concentrations. Her paralysis was maintained with a continuous infusion of cisatracurium. Continuous EEG monitoring demonstrated no evidence of seizure activity. On hospital days 5 and 4 of hypothermia, a repeat CT scan was obtained which showed improvement in cerebral edema (Fig. 4). On day 5 of hypothermia, a trial of re-warming was undertaken at a rate of 1°F/h to a goal temperature of 97°F which the patient tolerated. During this time her liver functions and coagulopathy had improved markedly and her ammonia levels had declined. CVVH was discontinued. The ICP monitor was discontinued 24 h after re-warming. Following this intervention, her sedation and paralytics were weaned off and she was successfully liberated from the ventilator on hospital day 11. Her liver function normalized and she had no neurological sequela prior to discharge. To our knowledge, this is the first reported case where hypothermia was maintained for 5 days for cerebral edema complicating FHF, with the patient having complete neurological and hepatic recovery.

Discussion

The development of hepatic encephalopathy in patients with FHF defines a turning point in the clinical course and portends a grave prognosis with a high mortality rate [2]. Hepatic encephalopathy is commonly complicated by the presence of cerebral edema and intracranial hypertension leading to brain herniation and death. Although data on the impact of elevated ICP on survival in liver failure are scant, a mortality of more than 90% is expected in patients whose

Fig. 2 Correlation of ICPs (cm H$_2$O) and temperature (°F), and arterial ammonia levels. Arterial ammonia levels are in meq/dl
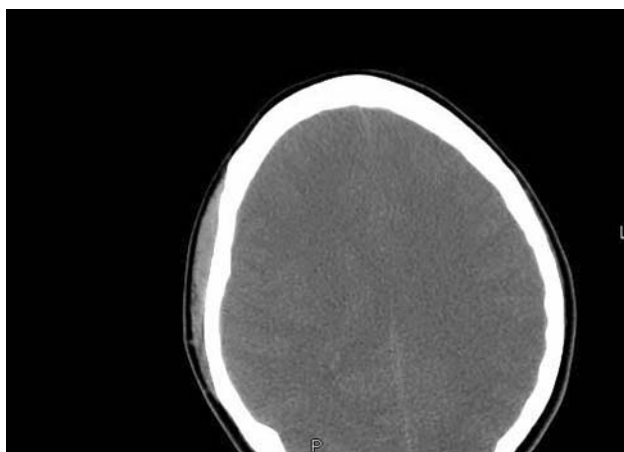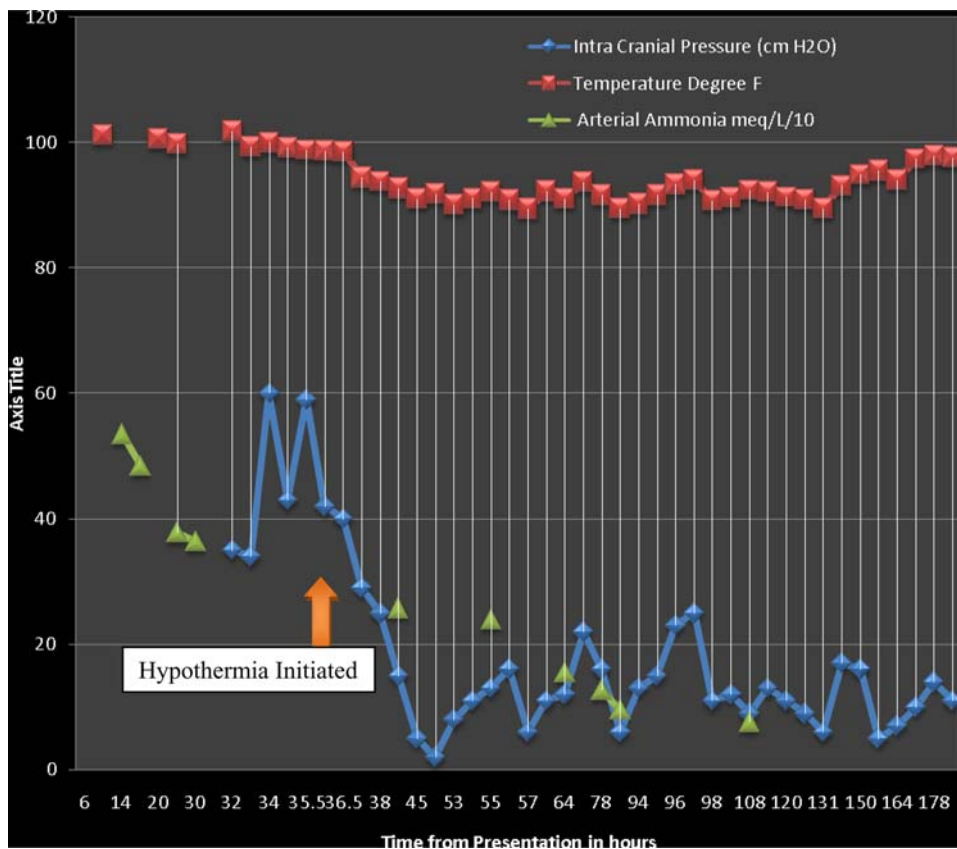

Fig. 3 Repeat CT scan of brain on day 4 showing worsening cerebral edema

Fig. 4 Repeat CT scan of brain on day 8 showing improvement in cerebral edema

ICP cannot be controlled by conventional means [3]. Indeed in a study of 315 patients with acute liver injury secondary to Tylenol overdose, 50% of deaths in the group that did not meet liver transplantation criteria and were deemed to have a good prognosis otherwise, expired from cerebral herniation [2]. These data suggest that brain herniation can occur even in those whose liver is recovering. The only definitive treatment for patients whose hepatic function is unlikely to recover is liver transplantation [4].

It is thus imperative to aggressively control ICP in patients who are suitable transplantation candidates as a bridge to liver transplant. This intervention also permits those who have a good prognosis adequate time for hepatic recovery.

Our patient had a predicted 30-day mortality risk of 85% without emergent liver transplantation based on Kings College Criteria and initial blood lactate levels and

mortality risk of 90% when 12-h post-resuscitation lactate levels were included to the risk assessment [5].

The pathogenesis of cerebral edema and intracranial hypertension associated with FHF is multifactorial, and not fully understood [6]. Cytotoxic mechanisms are thought to be key factors for the development of cerebral edema. Indeed in a recent study of seven patients with FHF and stage 3 or 4 encephalopathy, MRI with diffusion-weighted images demonstrated restricted diffusion which suggests cytotoxic edema [7]. A vasogenic component resulting from a leaky blood brain barrier from the effects of endotoxin or pro-inflammatory cytokines has also been proposed [8]. The predominant explanation of cytotoxic edema in FHF revolves around the ammonia glutamine hypothesis [9]. Excess ammonia secondary to a failing liver crosses the blood brain barrier and is converted to glutamine by the astrocytes. The link between hyperammonemia, glutamine, and elevated ICP was recently demonstrated in humans [9]. Elevated ammonia and glutamine levels cause osmotic and other complex effects on the astrocytes, leading to the development of cerebral edema. A growing body of literature links hyperammonemia with the development of cerebral edema in FHF. Patients with FHF and arterial ammonia level >150 μmol/l had a much higher likelihood of developing cerebral edema than those with lower levels; moreover, levels of >200 μmol/dl were associated with cerebral herniation [10].

The development of intracranial hypertension in FHF involves both cerebral edema and increased intracranial blood volume. The increase in blood volume involves an impairment of cerebral auto-regulation, leading to cerebral vasodilatation and an increase in cerebral blood flow (CBF) [11]. The exact mechanism of increased CBF remains unexplained but inflammatory cytokines [12] and the systemic inflammatory response syndrome are thought to be involved.

Current modalities of treatment of cerebral edema in FHF include elevation of head of the bed, hyperventilation, hyperosmolar therapy with either mannitol or hypertonic saline, and induction of barbiturate comas [13]. The use of mannitol can be limited by the development of acute renal failure and oliguria. To use mannitol repeatedly fluid can be taken off via hemofiltration, and this maneuver in itself has an ICP lowering effect. Although ammonia is thought to be central to the development of cerebral edema, ammonia lowering therapies have not been formally studied in patients with FHF. Ammonia can be lowered by dialytic methods [14] usually continuous venoveonous hemofiltration to avoid rapid fluid shifts. In our patient, it is likely that ammonia clearance by CVVH helped decrease her ammonia levels thereby, helping control of her ICP. Fewer data are available on the beneficial effects of NAC

[15], propofol, phenytoin, indomethacin, and artificial liver assist devices. Many of these modalities are difficult to implement because of relative contra-indications, lack of efficacy, and lack of availability.

There is an emerging body of literature that supports the use of mild-to-moderate therapeutic hypothermia (89.6–93.2°F) for the therapy of cerebral edema and intracranial hypertension associated with FHF. Therapeutic hypothermia decreases cerebral edema by multiple mechanisms [16]. The beneficial effects of hypothermia in FHF include decreasing the brain as well as arterial concentration of ammonia, improving osmotic disturbances in the brain, improvement in cerebrovascular dynamics, prevention of cerebral hyperemia, restoration of cerebral auto regulation, and decrease in pro-inflammatory cytokines [17]. The rapid decrease in ICP after initiation of hypothermia is paralleled by decreases in CBF and brain uptake of ammonia. There is also restoration of cerebral auto regulation and reactivity of the cerebral vasculature to carbon dioxide. These findings suggest that modulation of CBF and intracranial volume is a major protective mechanism [18]. There is a correlation between decreases in pro-inflammatory cytokines and reductions in CBF and ICP in FHF [19]. In a clinical study of hypothermia for intracranial hypertension and FHF, reduction in ICP was accompanied by both reduction in arterial concentration and brain flux of inflammatory cytokines and improved cerebral hyperemia. In a study of rats with liver injury secondary to acetaminophen, mild hypothermia improved survival, decreased hepatic apoptosis, attenuated liver injury, and did not adversely affect liver regeneration [20].

Potential adverse effects of mild hypothermia in acute liver failure include shivering, increased risk of infections, coagulopathy, cardiac ischemia, arrhythmias, hyperglycemia, and hyperlactatemia [21].

We believe that rapidly controlling our patient's ICP with therapeutic hypothermia allowed time for other therapies to work and allowed her to recover.

In conclusion, mild-to-moderate hypothermia appears to be an effective treatment for the treatment of cerebral edema and intracranial hypertension associated with FHF associated with acetaminophen overdose. We assume continued conventional medical therapies, including treatment of FHF and control of ICP had a significant role in this patient's recovery. Prolonged hypothermia can be used as a tool to control cerebral edema and ICP while awaiting liver recovery or as a bridge to transplantation. Rigorously performed randomized controlled trials are warranted to confirm the effects of hypothermia on FHF.

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