THERAPEUTIC HYPOTHERMIA FOR TREATMENT OF INTRACTABLE INTRACRANIAL HYPERTENSION AFTER LIVER TRANSPLANTATION

By Daniel N. Holena, MD, Nikolai S. Tolstoy, BS, Angela M. Mills, MD, Adam D. Fox, DO, and Joshua M. Levine, MD

Abstract
A comatose 23-year-old woman with acute liver failure due to an overdose of acetaminophen had indications of intracranial hypertension and underwent liver transplantation. Her level of arousal did not improve, and on postoperative day 1, clinical signs of cerebral herniation became apparent. An intracranial pressure monitor was placed, and intracranial hypertension was documented. Elevations in intracranial pressure persisted despite maximal osmotherapy, and therapeutic hypothermia was started. Normalization of intracranial pressure was rapid. Findings on neurological examination improved and the patient was discharged from the hospital with no neurological impairment. (American Journal of Critical Care. 2012;21:75,72-74)

A 23-year-old woman was admitted to our medical intensive care unit from an outside hospital. She had acute liver failure after ingesting approximately 90 tablets of oxycodone/acetaminophen and an unknown quantity of benzodiazepines. She arrived comatose at the outside hospital and was promptly intubated for airway protection. On initial examination, heart rate was 93/min, and blood pressure was 130/90 mm Hg. Her score on the Glasgow Coma Scale was 3T; her pupils were constricted but equal and reactive to light. The patient was given intravenous N-acetylcysteine for an initial acetaminophen level of 212 µg/mL (to convert to micromoles per liter, multiply by 6.614). During the next 48 hours, fulminant hepatic failure developed. Laboratory findings were as follows:

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The patient was transferred to the medical intensive care unit at our institution for evaluation for liver transplantation. On arrival, she was comatose, with pupils 3 mm, round, and sluggishly reactive. Her eyes were deviated down. Corneal, oculocephalic, and gag reflexes were normal. Computed tomography of the head showed diffuse cerebral edema without clear evidence of herniation. The patient had clonic contractions of the right forearm and was treated empirically with antiepileptic drugs (levetiracetam and phenobarbital). Lactulose was administered to treat a serum ammonia level of 161 µmol/L, and continuous venovenous hemofiltration was started to treat anuric renal failure. Boluses of mannitol were administered empirically for intracranial hypertension.

Within 24 hours, a donor liver became available, and the patient underwent orthotopic liver transplantation. After an unremarkable operative course, she was taken to the surgical intensive care unit for recovery. Postoperatively, the donor liver had good function, as evidenced by decreases in enzyme levels in liver function tests and normalization of coagulation parameters, but the patient remained comatose. An electroencephalogram showed no seizure activity, and repeat computed tomography showed stable diffuse edema with effacement of the basal cisterns consistent with early uncal herniation.

On postoperative day 2, progressive bradycardia and hypertension developed. Initial therapy consisted of elevation of the head of the bed, pain control, and sedation. Osmotherapy with mannitol was instituted, and a neurocritical care consultation was obtained. The patient was comatose (score on Glasgow Coma Scale, 3T). Her pupils were ovoid, equal, and sluggishly reactive. She had a forced downward gaze. Corneal, cough, gag, and oculocephalic reflexes were normal. After correction of thrombocytopenia, an intraparenchymal fiber-optic intracranial pressure (ICP) monitor (Camino, Integra Neurosciences, Plainsboro, New Jersey) was placed. The initial ICP was 35 mm Hg, and the pressure remained elevated (>20 mm Hg) despite treatment with an infusion of hypertonic saline (3% sodium chloride solution). Therapeutic hypothermia was started to treat refractory intracranial hypertension. The patient was cooled to 33ºC over 8 hours with boluses of cold saline and a surface cooling device (Arctic Sun, Medivance Inc, Louisville, Colorado). Core body temperature was measured by using an esophageal temperature probe (Esophageal Stethoscope 400 series, Shore Medical Incorporated, Orange, California). With hypothermia, the patient’s ICP steadily decreased to 7 mm Hg (see Figure). Vital signs normalized to heart rate approximately 70/min and systolic blood pressure approximately 140 mm Hg. After 48 hours of hypothermia, controlled rewarming (0.25ºC/h) was implemented until a core body temperature of 36.5ºC was reached. No further increases in ICP were observed. On postoperative day 4, the patient began to open her eyes spontaneously and follow commands; she was discharged from the intensive care unit on postoperative day 16.

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day 30, she was discharged home; she had no neurological impairments.

Discussion

Cerebral edema and resultant intracranial hypertension are recognized sequelae of acute liver failure and often lead to cerebral herniation and death if unchecked. Causes of cerebral edema include disruption of the blood-brain barrier by ammonia-induced inflammatory cytokines, increases in cerebrovascular blood volume due to cerebral vasodilatation or loss of autoregulation, and increases in brain tissue osmolality. Conventional medical therapy for intracranial hypertension in patients with acute liver failure consists of supportive care for hepatic failure and osmotherapy to reduce ICP. Mannitol has been used since the 1980s, and treatment with hypertonic saline may be useful.

Induction of barbiturate coma and administration of indomethacin have been used with variable success to treat intracranial hypertension refractory to osmotic agents. Some patients with acute liver failure and intracranial hypertension are candidates for orthotopic liver transplantation. Survival rates in patients who receive a liver transplant to treat acute liver failure are as high as 80% compared with roughly 20% in patients who do not receive a transplant. Intracranial hypertension usually resolves after orthotopic liver transplantation; however, if the hypertension persists, it can lead to permanent neurological injury or death in up to 10% of cases.

Therapeutic hypothermia has been used to treat refractory intracranial hypertension in patients with traumatic brain injury, and its use to control ICP in patients with acute liver failure who are undergoing transplantation has been described. In 2003, Jalan et al reported a case series of patients who were treated with preoperative and intraoperative hypothermia for severe intracranial hypertension refractory to conventional therapies. Effects on ICP, cerebral perfusion pressure, and vasopressor requirements were beneficial. Of note, in this small series, hypothermia to a median core temperature of 33.4°C was instituted preoperatively and was continued until transplantation of the graft. The mechanism through which hypothermia reduces ICP in patients with acute liver failure is currently under investigation, and various mechanisms have been proposed: suppression of cerebral metabolic rate, beneficial effects on ammonia metabolism, improvements in cerebrovascular hemodynamic status, and decreases in inflammatory mediators.

Although perioperative hypothermia may control elevated ICP in patients who have liver transplantation, hypothermia for refractory postoperative ICP has not been reported. One explanation is that acute liver failure that requires transplantation is relatively rare, and when a patient with acute liver failure has elevated ICP, the pressure typically resolves after engraftment. Also, concerns that hypothermia may be detrimental during surgery may dissuade clinicians from using this treatment. The general surgical literature is replete with studies on the detrimental effects of perioperative hypothermia, including increased rates of infection at the surgical site, blood loss, and cardiac events. In patients with orthotopic liver transplants, perioperative hypothermia has been associated with an increased risk for cytomegalovirus infection and mortality after transplantation. Deliberately induced hypothermia also may be associated with risks specific to the technique used for induction; use of intravascular cooling devices has been associated with cerebral vasospasm and thrombosis.

Perhaps the greatest concern about perioperative hypothermia is that the treatment may exacerbate coagulopathy and lead to hemorrhage. Orthotopic liver transplant patients are unique. In addition to the elevated prothrombin times and thrombocytopenia common in end-stage liver disease, they also have the inherent risk for postoperative bleeding associated with major abdominal surgery. Although our patient had no evidence of bleeding or infection at the surgical site during or after hypothermia, she did experience 2 postoperative infectious complications: ventilator-associated pneumonia and urinary tract infection.

Because of the risks of hypothermia after other types of surgery and the lack of data on the safety and efficacy of this treatment in patients who have orthotopic liver transplantation, use of therapeutic hypothermia for intracranial hypertension after transplantation must be considered cautiously after careful deliberation of the possible risks and benefits. Communication between transplant surgery, intensive care, and neurology teams is mandatory. In the case we report, therapeutic hypothermia successfully lowered the patient’s ICP after conventional treatment was unsuccessful, allowing her to make a complete recovery.

FINANCIAL DISCLOSURES
None reported.

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