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Therapeutic hypothermia as a bridge to transplantation in patients with fulminant hepatic failure

Hipotermia terapêutica como ponte até transplante em pacientes com falência hepática fulminante

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ABSTRACT

The most important topics in fulminant hepatic failure are cerebral edema and intracranial hypertension. Among all therapeutic options, systemic induced hypothermia to 33 - 34°C has been reported to reduce the high

pressure and increase the time during which patients can tolerate a graft. This review discusses the indications and adverse effects of hypothermia.

Keywords: Hypothermia; Transplantation; Liver failure, acute

INTRODUCTION

Malignant brain edema associated with hepatic encephalopathy is an important cause of death in fulminant acute liver failure (ALF).⁽¹⁾ To date, no specific treatment has been shown to prevent the development of brain edema, intracranial hypertension and brain herniation (Figure 1). Orthotopic liver transplantation (OLT) is the only accepted treatment for this condition, but many patients die while waiting for a suitable organ donor.^(2,3)

Early diagnosis and management of hepatic encephalopathy are critical to prevent or allow time for liver transplantation. Several general measures are initiated once grade III - IV encephalopathy develops, including ventilator support, deep sedation and the use of mannitol or hypertonic saline. Bridge techniques to OLT, such as bio artificial livers and hepatocyte transplantation, are still experimental.^(2,4)

Therapeutic mild hypothermia has unique advantages in this setting because it reduces high intracranial pressure and may prevent irreversible neuronal damage until a donor liver becomes available or spontaneous recovery occurs. In the present article, we will discuss the role of hypothermia in patients with fulminant hepatic failure and coma and suggest an algorithm for its implementation. We searched the literature using MedLine and the National Institutes of Health/National Library of Medicine through 2013. The following search terms were used: acute liver failure or fulminant hepatic failure with therapy and hypothermia. No limitation for publication date was used.

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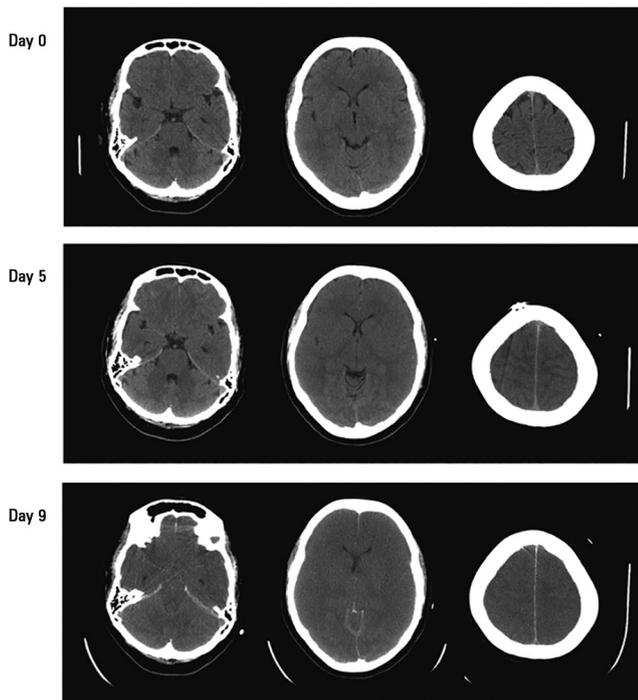


Figure 1 - Sequential computed tomography of the brain in a 37 year old female patient admitted due to acute liver failure, hepatic encephalopathy and the need for ventilatory support. The patient showed a normal computed tomography scan on admission. On the fifth day, there was a marked loss of the normal sulci pattern. As malignant brain edema progressed, the loss of normal grey/white differentiation was noted, and a marked loss of the basal cisterns and brainstem compression were observed. The patient was refractory to medical treatment and died while waiting for a donor.

Pathophysiological concepts in hepatic encephalopathy

Episodes of intracranial hypertension may be detected during the course of ALF in 80% to 95% of patients with stage III-IV hepatic encephalopathy undergoing intracranial pressure (ICP) monitoring.^(5,6) High ICP remains responsible for substantial mortality (25 - 50%) and neurocognitive sequelae in patients surviving ALF,^(3,5,7-9) thus justifying the need for more effective therapies.

Hepatic encephalopathy is most likely due to several mechanisms that are not fully understood, including the accumulation of ammonia and glutamine, which affect brain metabolism and function. During ALF, a direct relationship exists between the levels of ammonia, encephalopathy and cerebral herniation.^(8,10-12) Inside the astrocytes, the excess ammonia is metabolized to glutamine, which increases the osmolar load and

promotes the entrance of water into the cells.⁽¹³⁾ Other proinflammatory mediators and cytokines shown to be increased in the course of ALF might have permissive or direct effects on the development of hepatic encephalopathy.⁽³⁾

An increase in cerebral blood flow (CBF) has also been identified early in the course of patients with ALF and brain edema.⁽⁷⁾ Several mechanisms have been implied, including increased production of nitric oxide, prostaglandins, and proinflammatory mediators. Failure of CBF auto regulation is typically observed late during the course of hepatic encephalopathy.

Effects of hypothermia on the brain

Several experimental models and human clinical trials performed in different clinical settings have demonstrated that lowering the body core temperature may benefit the brain.⁽¹⁴⁾ In fact, moderate hypothermia is routinely performed to protect the brain during cardiac surgery. However, it has only recently been shown that hypothermia can increase the likelihood of neurologically intact survival in patients with cardiac arrest.^(15,16) Currently, hypothermia has gained popularity as a brain protective strategy for comatose survivors of sudden cardiac death.^(14,17)

Recently, a study comparing a strategy of targeted temperature maintenance at 36°C versus hypothermia (33°C) in 950 patients with coma after cardiac arrest showed no major differences in all-cause mortality between both strategies.⁽¹⁸⁾ Although the concept of targeted temperature is attractive because it avoids fever, the 2010 American Heart Association Guidelines still recommend hypothermia between 32°C to 34°C for 12 to 24 hours in comatose adult patients after cardiac arrest.⁽¹⁹⁻²¹⁾

During ALF, the pathophysiology of brain edema and the goals of hypothermia are different than those of hypoxic encephalopathy. Hypothermia is not focused on fever control; it is used to prevent or control intracranial hypertension and reduce the toxic effects of ALF on the brain. With this therapeutic objective in mind, we expect to prolong the wait time before liver transplantation.

The protective effect of hypothermia has been traditionally attributed to a reduction in the metabolic rate, and hence a reduction in oxygen consumption

and glucose utilization. For each 1°C decrease in core temperature, the cerebral metabolic rate decreases by 6% to 7%.⁽¹⁴⁾ Hypothermia also protects the cell by maintaining the integrity of the lipoprotein membrane and decreasing enzymatic reactions that lead to cell damage or death.

Mild hypothermia can also reduce intracranial pressure and has been shown to decrease CBF due to cerebral vasoconstriction.⁽²²⁾ This protective effect decreases intracranial pressure and may also act as an anticonvulsant.⁽²³⁾ However, multicenter clinical trials evaluating hypothermia in traumatic brain injury have yielded conflicting results.⁽²⁴⁻²⁶⁾

Therapeutic hypothermia is also used in many other clinical scenarios without demonstrated benefit, including stroke, near-drowning, spinal cord ischemia, and status epilepticus, among others.^(23,27,28)

Bradycardia is associated with hypertension and cardiac arrhythmias, which are known side effects of hypothermia. Hypothermia may induce coagulation abnormalities and increase the risk of infections, particularly pneumonia. Additionally, electrolyte disorders and hyperglycemia have been reported. Most complications of hypothermia are easily preventable with good intensive care and should not limit its use when indicated.^(4,22,27)

Experimental trials of hypothermia in acute liver failure

Mild hypothermia prevents the development of brain edema and intracranial hypertension in experimental models of ALF, possibly by preventing hyperemia, altering brain ammonia or glucose metabolism, or by a combined effect.^(4,29,30) Hypothermia therapy also improves survival and the neurological outcome in animal models of acute liver failure.^(31,32) No other intervention has the ability of hypothermia to prevent the cerebral complications of ALF in such a systematic and reproducible way, most likely due to the multiple pathogenetic mechanisms involved, as opposed to single targets affected by other measures.^(9,30)

However, direct extrapolation of animal findings to the human condition is limited due to interspecies differences in the pathophysiology of ALF.⁽⁹⁾ Experimental models in small rodents do not reproduce all aspects of human ALF, including its multiple causes, as well as

systemic complications such as sepsis, respiratory failure or renal failure. Additionally, technical aspects, including the effects of rewarming, cannot be easily applied to the clinical setting.

Clinical data of hypothermia in acute liver failure

Moderate hypothermia (32 - 34°C) may prevent or control intracranial hypertension (ICH) in patients with ALF. Several clinical reports and non-controlled trials suggest that mild hypothermia may improve outcomes.⁽³³⁻³⁶⁾

The first series included seven patients with ALF and refractory intracranial hypertension.⁽³⁶⁾ Four patients were successfully transplanted after 10-14 hours of mild hypothermia (32 - 33°C), while three patients who were unsuitable candidates for OLT died after rewarming. Years later, the same author reported 14 patients with ALF and increased ICP, of which 13 could be transplanted after a median of 32 hours (range, 10 - 118 hours) of cooling.⁽³⁵⁾

Hypothermia likely reduces ICP by impacting multiple mechanisms. Hypothermia produces a sustained and significant reduction in arterial ammonia concentration, cerebral blood flow, brain cytokine production, and markers of oxidative stress.⁽³⁵⁾ It may also prevent cerebral hyperemia and increases in intracranial pressure during liver transplantation.⁽⁵⁾

A recent prospective, randomized, controlled, multicenter trial (not published yet) evaluated 54 patients with ALF, imminent brain edema and intracranial pressure (ICP) monitoring.⁽³⁷⁾ The patients were randomized to receive standard medical therapy (33 patients) or moderate hypothermia (33.2 ± 0.7°C) for 3 consecutive days (21 patients). Intracranial hypertension (ICP > 25mmHg) was observed in nearly half of the patients (57% hypothermia versus 45% control, $p = 0.58$), but there were no differences in mortality (48% hypothermia versus 58% control) or in the incidence of adverse events in the two groups.

Unanswered question

Several issues remain unanswered in the management of hepatic encephalopathy during ALF. Once stupor or coma develops, mechanical support utilizing a protocol for protecting the brain from malignant edema is mandatory (Figure 2). Most centers will agree in the use

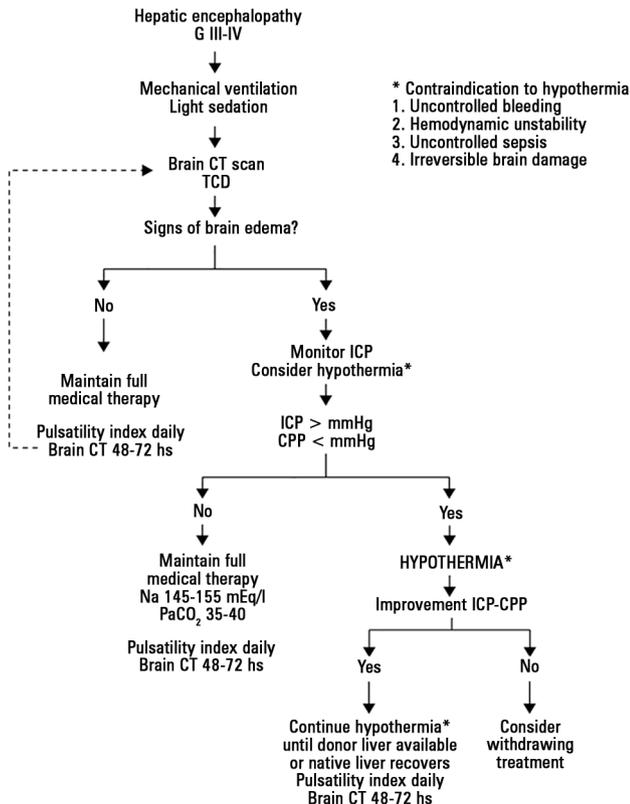


Figure 2 - Suggested algorithm for managing acute liver failure and hepatic encephalopathy. Therapeutic hypothermia is considered when early signs of brain edema appear on a computed tomography scan, ideally under intracranial pressure monitoring. CT - computed tomography; TCD - transcranial Doppler; ICP - intracranial pressure; CPP - cerebral perfusion pressure; Na - sodium plasma levels; PaCO₂ - partial pressure of carbon dioxide.

of mannitol or hypertonic saline, mild hyperventilation, light sedation, or vasoactive agents for preventing hypotension.⁽⁶⁾ However, the timing and targets of these therapies, as well as the usefulness of monitoring ICP and CPP, are controversial issues.

In our country, where the waiting time for a liver donor is well beyond 48 hours, the necessity of delaying the natural evolution of brain edema is crucial. Available liver support systems have mostly failed in the treatment of ALF and are still not recommended outside of clinical trials.^(2,4) In contrast, therapeutic hypothermia has been shown to prevent or control intracranial hypertension in experimental models and clinical studies of ALF. Despite the absence of controlled trials showing improved outcomes in this setting, a better selection of patients and new technological advances for the implementation of hypothermia may produce better clinical results and buy time until a liver donor becomes available.

CONCLUSION

At this time, and before a better clinical evidence becomes available, the use of therapeutic hypothermia in patients with acute liver failure can only be recommended as an active measure when intracranial hypertension cannot be controlled by full medical conventional treatment.

RESUMO

Os tópicos mais importantes na falência hepática fulminante são o edema cerebral e a hipertensão intracraniana. Dentre todas as opções terapêuticas, tem sido relatado que a hipotermia sistêmica induzida em níveis entre 33 - 34°C reduz a elevação da

pressão e aumenta o tempo durante o qual os pacientes podem tolerar um enxerto. Esta revisão discutiu as indicações e os efeitos adversos da hipotermia.

Descritores: Hipotermia; Transplante; Falência hepática aguda

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