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Hypothermia in Acute Liver Failure

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1. Introduction

Acute liver failure (ALF), the manifestation of severe hepatocellular injury in the absence of pre-existing liver disease is a catastrophic and frequently fatal disorder. Though the injury is potentially reversible, the clinical course often culminates in multiple organ failure which is associated with a poor prognosis. The incidence is between 1 and 6 per million population per year [1]. However this data is predominantly from developed countries, data from developing countries where the etiology of ALF is very different is virtually absent. The most common etiologies in the developing world are hepatotropic viruses (Hepatitis A, B and E) in comparison to drug induced liver failure which predominates in developed countries [2]. Amongst drugs, acetaminophen is the leading cause of acute liver failure and accounts for approximately 50% of the cases in the US [3]. Other etiologies include other viral infections and drugs, ischemic hepatitis, Wilson's disease, autoimmune hepatitis, pregnancy related liver disorders and a large sero-negative cohort where no inciting cause can be identified.

Originally the definition of acute liver failure encompassed the development of coagulopathy and encephalopathy within 8 weeks of the original hepatic insult [4]. Newer definitions differentiate between, hyper-acute, acute and sub-acute liver failure contingent on the time period between the onset of jaundice and the onset of encephalopathy [5]. Regardless of definition used, the onset of hepatic encephalopathy especially Grade III/IV encephalopathy defines a turning point in the clinical course of this disease [6]. Occurrence of hepatic encephalopathy or coma in ALF is a poor prognostic sign and is associated with the development of cerebral edema, intracranial hypertension and subsequent mortality from brain herniation [7]. Though advances in the care of the patient with ALF have led to both a decrease in the incidence and associated mortality of persons developing cerebral edema and intracranial hypertension [7], careful vigilance should be exercised because development and progression of encephalopathy can be rapid and fatal. Further data on the declining incidence and mortality are from a single tertiary care academic center with

immediate access to transplantation services. Such expertise may not be readily available at other facilities and therefore the outcomes at such centers could be considerably different. Moreover, cerebral edema and raised intracranial pressure in persons with ALF accounts for substantial mortality (between 25 and 50%) as well as neurocognitive sequelae in survivors.

Given the devastating consequences of development of raised ICP in patients with ALF, it is imperative that early recognition and effective therapies be promptly instituted. Unfortunately prognosis in the absence of liver transplantation is dismal. Medical therapies are frequently utilized to control ICP as bridge to transplant. Often however medical therapies fail to adequately control ICP. Application of induced therapeutic hypothermia has shown promise in controlling ICP when medical therapies have failed. An increasing number of centers have incorporated hypothermia into their armamentarium of therapies to treat raised ICP associated with ALF as a bridge to liver transplant [8]. Emerging data also suggests that this modality of treatment can successfully be used as a strategy to allow for hepatocellular regeneration and bridge patients with ALF and cerebral edema to recovery [9, 10]. Timing of institution, identification of sub groups that benefit and guidelines for use in this condition remain unclear. This aim of this review is to highlight the pathogenesis of cerebral edema and attempt to elucidate the role of hypothermia in patients with ALF.

2. Pathophysiology of cerebral edema and intracranial hypertension in acute liver failure

2.1. Development of cerebral edema

The exact pathophysiological mechanisms responsible for the occurrence of cerebral edema as a devastating complication of ALF are not completely elucidated. Cytotoxic edema appears to be the major mechanism involved in the development of cerebral edema [11, 12], though newer data suggest a role for vasogenic edema as well [13, 14]. Cytotoxic injury secondary to cellular energy failure, impaired cellular metabolism and osmoregulation culminates in swelling of cellular elements and accumulation of water mainly in grey matter. These changes involve astrocytes, microglia and neurons; however astrocyte swelling is a common neuropathological feature of cerebral edema in ALF. Vasogenic edema results as a consequence disruption of the blood brain barrier leading to leakage of plasma into the interstitial space and water accumulation in white matter.

Ammonia is thought to play a central role for cytotoxic injury in this regard and is thought to be the most important factor leading to the formation of brain edema [15]. In animal models, the inhibition of glutamine synthetase, the primary brain enzyme capable of metabolizing free ammonia prevents formation of cerebral edema, despite further increases in brain and plasma ammonia levels [16]. In conditions of acute liver failure, ammonia levels rise in the plasma and astrocytes. In the astrocytes by the process of amidation, ammonia combines with glutamate to produce glutamine, a reaction catalyzed by glutamine synthetase [17]. Accumulation of glutamine along with hyperammonemia in astrocytes leads to osmotic alterations, oxidative stress, changes in the mitochondrial permeability transition, free radical production and

alterations in brain glucose metabolism. Together these mechanisms lead to accumulation of brain water and astrocyte swelling [18]. Though the aforementioned cytotoxic mechanisms predominate, an increasing role of vasogenic edema contributing to increased brain water and consequent raised intracranial pressure has been recently recognized. Although structurally normal the blood brain barrier becomes selectively leaky to certain polar molecules through subtle perturbations of the tight junctions [19].

2.2. Cerebral blood flow

Cerebral blood flow is often dysregulated in ALF. Loss of auto-regulation [20] and cerebral hyperemia [21] are two common manifestations of ALF and encephalopathy. Systemic inflammatory response syndrome, particularly tumor necrosis factor has been shown to correlate with development of encephalopathy and raised intracranial pressure [22]. Cerebral hyperemia may also contribute to the development of cerebral edema.

2.3. Raised intracranial pressure

The combination of cerebral edema and increased cerebral blood volume from dysregulated cerebral blood flow lead to increased intracranial pressure in ALF.

2.4. Clinical correlates

Arterial ammonia concentrations greater than 100 $\mu\text{mol/L}$ predict the onset of hepatic encephalopathy [23] and concentrations greater than 200 $\mu\text{mol/L}$ are associated with the development of intracranial hypertension and subsequent brain herniation [24]. Younger age, development of renal failure, hyponatremia, inflammatory response and the need for hemodynamic support for cardiovascular collapse are additional risk factors associated with the development of intracranial hypertension [24]. Similarly higher cerebral blood flow rates are seen in patients with cerebral edema and intracranial hypertension and are associated with higher mortality [21].

3. The role of hypothermia

A growing body of experimental data and clinical data promotes the concept that induction of mild hypothermia (between 32 and 35 degrees centigrade) is an important therapy in the armamentarium against the development of cerebral edema and intracranial hypertension in fulminant hepatic failure. Hypothermia has been shown to either attenuate or reverse most pathophysiological pathways involved in the development of cerebral edema in ALF.

3.1. Mechanism of hypothermia

In the context of liver injury, hypothermia was first shown to be efficacious in 1962 against the toxicity of acute ammonia loading in mice [25]. Thereafter, Traber et al demonstrated that spontaneous development of hypothermia in a rat model of ALF was associated with

significant reductions in both cerebral edema and the time to develop encephalopathy in comparison to rats maintained at normal temperature [26]. This phenomenon has now been demonstrated in a variety of other animal models of ALF [27]. The ability of hypothermia to favorably affect multiple pathways of injury is probably responsible for its remarkable and reproducible effects on reductions of cerebrovascular complications of experimental ALF.

The major explanatory mechanisms for the efficacy of hypothermia probably involve reductions in systemic and brain ammonia concentrations as well as reductions in cerebral blood flow. Nevertheless a variety of systemic and cerebrovascular beneficial effects have been proposed.

3.2. Cerebrovascular effects

Hypothermia, in the absence of changes in circulating concentrations of ammonia, independently causes lowering of brain and cerebrospinal fluid ammonia levels in mice [28]. Hyperammonemia in the brain causes abnormal brain metabolism of glucose, increased glutamine synthesis and increased oxidative stress. Abnormalities in glucose metabolism lead to flux down the glycolytic pathway and increased synthesis of lactate. In an animal model of ALF, inducing hypothermia eliminated the increased lactate and alanine production before decreasing cerebral edema [29]. These observations suggest that hypothermia mitigates abnormalities of glucose metabolism in the brain [30]. Although glutamine has been proposed to be the key metabolite of ammonia metabolism responsible for osmotic disturbances and water accumulation in the brain, prevention of brain edema by hypothermia was not accompanied by reductions in brain glutamine in experimental models of ALF. However other disturbances in other osmolytes such as myo-inositol, taurine, glutamate, lactate and alanine were significantly improved, leading to a better osmotic environment in the brain [28, 29]. Hypothermia in animal models has also lead to the decrement of glutamate and other amino acids in the extracellular compartment of the brain. Brain glutamate is known to increase in both patients [31] and in experimental ALF [32]. Additionally hypothermia has important anti-inflammatory properties. Inflammatory mediators may incrementally enhance the toxicity of ammonia resulting in worsening cerebral edema. Protein and m-RNA markers of a variety of pro-inflammatory cytokines such as IL-1 beta, TNF alpha and IL-6 have been reported to be increased in the brain of rats with hepatic devascularization at the time of cerebral edema [33]. Hypothermia has been associated with the diminution of brain efflux of such cytokines in patients and attenuation of cytokine production and brain edema in animals [34]. Finally reductions in body temperature have led to reduced markers of brain oxidative and nitrosative stress in animal models of ALF [35].

Adverse consequences of ALF on cerebrovascular hemodynamics include increased cerebral blood flow and loss of cerebrovascular auto-regulation. Increases in cerebral blood flow are both absolute as well as relative to cerebral metabolic demand. These alterations play a role in the development of cerebral edema and increased ICP in ALF. Therapeutic hypothermia reverses the increments in cerebral blood flow and restores auto-regulation in patients with

ALF. Hypothermia in patients with cerebral edema and raised ICP refractory to conventional medical therapy not only lowered ICP but also restored cerebrovascular auto-regulation to changes in mean arterial pressure and reestablished the vasodilatory response to changes in partial pressure of carbon dioxide [36].

3.3. Systemic effects

Hypothermia consistently lowers circulating ammonia concentrations in humans and in animal models of ALF. In one experimental model, systemic ammonia concentrations were lowered by hypothermia even when hepatic detoxification was bypassed. These observation suggest that production of ammonia is reliant on temperature and that mechanisms of production are perhaps more sensitive to hypothermia than are those involved in detoxification.

ALF is characterized by distributive physiology leading to elevated cardiac output and low systemic vascular resistance [37]. Activation of the systemic inflammatory response syndrome plays a pivotal role in the hemodynamic derangements of ALF [38]. Inflammation acts synergistically with ammonia in the development of high ICP in persons with ALF possibly through modulation of cerebral blood flow [39]. Hypothermia decreases systemic pro-inflammatory cytokines in animal models as well as patients with ALF. Hypothermia also has beneficial effects on systemic hemodynamics; a clinical investigation in persons with ALF and high ICP revealed that induction of hypothermia reduced cardiac output and raised systemic vascular resistance leading to diminished vasopressor requirements [40]. Thus by its potential of affecting both systemic hemodynamics and inflammation, hypothermia attenuates adverse consequences of these derangements on cerebrovascular hemodynamics.

Beneficial Effects	Potential Deleterious Effects
<ul style="list-style-type: none"> Improvement in cerebral edema and decreases in intracranial pressure Decreases in brain ammonia concentration and uptake Attenuation of brain osmolyte imbalances, oxidative stress and inflammatory markers Decreases in cerebral blood flow and prevention of cerebral hyperemia Restoration of cerebral blood flow auto-regulation Decreases in systemic circulating ammonia concentration and inflammatory markers Improvements in systemic hemodynamic alterations Attenuation of deleterious effects of ischemia reperfusion injury to liver Decreased inter-organ ammonia production and trafficking 	<ul style="list-style-type: none"> Increases in cerebral blood flow and rebound increases in ICP especially during rewarming phases Increased risk of infections Increased risk of bleeding complications Cardiac arrhythmias Fluid and electrolyte shifts

Table 1. Brief Summary of the Effects of Hypothermia

Hypothermia may also attenuate liver injury. Hepatoprotective effects of hypothermia have consistently been demonstrated in hepatic ischemia perfusion models [41]. Reductions in metabolic demand, tempering of free radical production, lessening of inflammatory cytokines, preservation of sinusoidal cell function and improvements in the hepatic microcirculation are some of hepatoprotective mechanisms mediated by hypothermia. Similarly in a mouse model of acetaminophen induced liver injury, hypothermia attenuated hepatocyte damage and improved survival [42]. A brief summary of the effects of hypothermia is given in Table 1.

3.4. Clinical correlates

Despite the wealth of animal data, there has never been a randomized control trial of hypothermia for ALF. Most reports are from a single center and have small numbers of patients [9, 10, 36-40, 43, 44]. Jalan et al first reported a series of 7 patients with ALF who underwent hypothermia to control ICP that was refractory to medical therapy [43]. Survival was 75% (3/4) in patients who received a liver transplant while none of those who did not progress to transplant survived. However the 3 patients that were deemed unsuitable for receipt of a liver transplant were only cooled for 8 hours and were then rewarmed to baseline temperature in one hour. The same group of investigators in 2004 reported a series of 14 patients who were awaiting liver transplantation and had cerebral edema with increased ICP refractory to medical therapy. Therapeutic hypothermia was initiated and maintained during the surgical period. Remarkably the survival of this group of patients was 70% and the neurological recovery was reported to be complete [40]. Jalan et al have also reported a series of 16 patients undergoing liver transplantation out of which 5 had high ICP uncontrolled by conventional therapy [44]. The patients with high uncontrolled ICP underwent hypothermia which was maintained during the transplant surgery. Interestingly, all patients transplanted under normothermic conditions developed surges of high ICP during the dissection and reperfusion phases of the surgery related to cerebral hyperemia, whereas, this phenomenon was not observed in the hypothermia group. These observations are encouraging and support the use of therapeutic hypothermia in at least persons who develop cerebral edema as a complication of ALF and have raised ICP unresponsive to medical therapy. However confirmation of benefit requires a well done randomized controlled trial.

The first ever RCT was recently present in abstract form in 2011 [45]. In this trial, Larsen et al. included 54 patients with ALF, in whom a clinical decision for ICP monitoring (imminent brain edema) had been made. Patients were randomized to receive standard therapy or therapeutic hypothermia plus standard therapy. Hypothermia was continued for 3 days. The authors reported no differences in outcomes of mortality, complications or the number of patients who developed high ICP at some point during their clinical course (approximately 50%). Reconciliation of these results, with results of observational studies suggesting major benefit, arises from the fact that persons in this study were randomized to hypothermia prior to the development of uncontrolled intracranial hypertension as a pre-emptive measure. It is prudent to await the final results of this trial to provide important clinical direction in regards to defining the place of hypothermia in ALF.

The previous sections discussed the role of hypothermia in either patients who are candidates for liver transplantation and have high ICP that is poorly responsive to conventional medical therapy or in patients who are at high risk of developing intracranial hypertension associated with ALF. In such persons, hypothermia is used as a bridge to transplant. However, some reports are now emerging that suggest that this therapy maybe potentially be useful as a bridge to recovery in patients who are not candidates for liver transplantation or are at places where organs and/or transplant expertise is unavailable [9]. In previous investigations, rapid rewarming from hypothermia has been uniformly associated with rebound of high ICP, clinical deterioration and death [43]. Therefore instituting hypothermia as a bridge to recovery typically requires prolonged duration of therapy (> 100 hours) till liver recovery occurs and slow rewarming thereafter [9]. It should be the safety and efficacy of hypothermia in this particular group of patients has not been established and the evidence for use is circumspect at best. A summary of clinical studies examining the role and effect of hypothermia in acute liver failure is given in Table 2.

Reference	Description of Study	Outcome
Jalan R et al: Lancet 1999	ALF with refractory elevation of ICP (> 25 mm Hg). Total of 7 patients with 4 listed for transplant. Hypothermia (32-33.5 C) performed for 8-14 hours. Those not suitable for transplant were rewarmed over 1 hour to 37 C. Those suitable for transplant cooled through the transplant procedure	3/3 unsuitable candidates for transplant died after rewarming. 1/4 transplant candidates died. Hypothermia was effective in controlling ICP in all patients and during hypothermia there were no significant relapses of increased ICP
Jalan R et al: Hepatology 2001	ALF with uncontrolled intracranial hypertension. 9 patients were cooled and cerebral hemodynamics were evaluated pre and 4 hours post hypothermia (cerebral blood flow and its auto-regulation, reactivity to carbon dioxide and intracranial pressure)	Hypothermia significantly lowered ICP and cerebral blood flow. Hypothermia restored defective cerebral blood flow auto-regulation and loss of reactivity to carbon dioxide that were observed in all patients pre hypothermia
Jalan R et al: Transplantation 2003	16 patients undergoing liver transplant were studied and divided into three groups pre transplant: Group I - No therapy required for ICP (ICP < 15), Group II - ICP controlled with medical therapy and Group III - ICP uncontrolled by medical therapy and requiring induction of hypothermia pre transplant. Normothermia was maintained during transplant in Groups I and II and hypothermia (median temperature 33.4 C) for the Group III (n=5)	Significant increases in ICP were observed during the dissection and re-perfusion phase of transplant in Groups I and II accompanied by an increase in cerebral blood flow. In Group III neither increases in ICP nor cerebral blood flow were observed.

Reference	Description of Study	Outcome
Jalan R et al: Gastroenterology 2004	14 patients awaiting liver transplantation with increased ICP refractory to medical therapy. Hypothermia (32 – 33 C) performed for a median of 32 hours (range 10 – 118 hours) as a bridge to liver transplant.	13/14 patients successfully bridged to transplant. 1/14 taken of transplant list and subsequently died. Significant decline in ICP within first hour of cooling that was maintained at 24 hours. After transplant 10/13 patients alive at 3 months and had complete neurological recovery.
Jacob et al: Neurocritical care 2009	Single case report of ALF and cerebral edema secondary to acetaminophen toxicity with increased ICP refractory to medical therapy. Hypothermia induced for 5 days as a bridge to liver recovery.	Sustained decrease in ICP with induction of hypothermia that was maintained over the duration of hypothermia. Complete hepatic and neurological recovery reported
Castillo et al: 2009	Single case report of acute liver failure secondary to hepatitis A virus with cerebral edema and elevated ICP refractory to medical therapy. Hypothermia induced for 122 hours as bridge to liver transplant.	Decrease in ICP with successful bridge to and survival after liver transplant
Holena DN et al: American Journal of Critical Care 2012	Single case report of acetaminophen induced ALF who developed cerebral edema and elevated ICP refractory to medical therapy treated with hypothermia as a bridge to liver transplant.	Decrease in ICP with hypothermia, improvement in neurological examination and bridge to liver transplant. Re-transplanted secondary to acute rejection and made complete neurological recovery

Table 2. Clinical Studies Examining the Effect of Therapeutic Hypothermia in Acute Liver Failure

Unlike cardiac arrest several questions about the induction, maintenance and rewarming phases of hypothermia in ALF are unanswered. Though the general principles of adequate sedation, avoidance of shivering, hemodynamic and other organ system monitoring as well as attention to fluid and electrolyte shifts remain the same, there are many issues unique to the patient with ALF. Particularly appropriate patient selection, risks of ICP monitoring, severe coagulopathy in ALF that may potentially be worsened by hypothermia, risks of infection, worsening cardiovascular instability and the potential deleterious effect of hypothermia on liver regeneration are some of the challenges faced by the clinician prior to instituting this therapy. If hypothermia is instituted as a bridge to liver recovery and subsequent resolution cerebral edema, the authors suggest that hypothermia with ICP monitoring be continued till there is evidence of liver recovery and that rewarming proceed at no more than 0.1 degrees centigrade every 2-3 hours.

4. Conclusions

There is a growing body of pre-clinical and clinical literature on the utility of therapeutic hypothermia to control raised ICP associated with ALF. Hypothermia may be used either as a bridge to liver transplant or a bridge to liver recovery. However based on evidence at hand, it can only be recommended for control of intracranial hypertension that is unresponsive to conventional medical therapy. Well-designed clinical investigations are required to clarify the role of hypothermia in ALF.

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