

Therapeutic Hypothermia for Acute Liver Failure: Toward a Randomized, Controlled Trial in Patients with Advanced Hepatic Encephalopathy

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Abstract Acute liver failure (ALF), the abrupt loss of liver function in a patient without previous liver disease, remains a highly mortal condition. Patients with ALF often succumb to their liver injury after the development of cerebral edema, resulting in intracranial hypertension and brain herniation. While the management of cerebral edema in ALF always includes the administration of osmotically active agents, osmotherapy often reduces intracranial pressure (ICP) insufficiently, such that herniation may be delayed but not prevented. Therapeutic hypothermia, the intentional reduction of body core temperature, has been increasingly used to treat cerebral edema in patients with traumatic and hypoxic brain injury. Data in animal models of ALF also suggest that hypothermia is effective in the prevention and treatment of cerebral edema, and case reports in humans have suggested

that hypothermia is an effective bridge to orthotopic liver transplantation. A randomized, controlled trial comparing the management of ALF patients under normothermic and hypothermic conditions is a logical extension of these preliminary observations. Herein, we consider the many difficulties which will be encountered in the design of such a trial in patients with ALF at high risk of developing cerebral edema.

Keywords Cerebral edema · Hypothermia · Acute liver failure

Introduction

Acute liver failure (ALF) may be defined as the abrupt onset of severe liver injury, characterized by coagulopathy and hepatic encephalopathy, in a patient without pre-existing liver disease [1]. In the United States, approximately 2,000 cases of ALF occur yearly, of which almost 50% are due to acetaminophen (APAP) overdose. Many other etiologies (viruses, drugs, toxins, others) contribute to the overall number of cases, but individually, none more than 15% [2].

ALF remains a syndrome with very poor prognosis. In the US ALF Study Group Registry of more than 1,200 patients, approximately 33% died, 25% underwent orthotopic liver transplantation (OLT), and the remainder recovered spontaneously without OLT [2]. These statistics represent a considerable improvement over historical series, however, as a result of better intensive care management, liver organ allocation and OLT techniques, and the early administration of *N*-acetylcysteine (NAC) to patients with APAP overdose [3, 4]. Although ALF affects almost every organ system, its high mortality can be ascribed to three major complications: sepsis, multi-organ system failure (often triggered by sepsis),

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and brain herniation due to cerebral edema [5–8]. ALF patients at particularly high risk for developing cerebral edema include those with high grade hepatic encephalopathy [9], high serum ammonia concentrations [5, 6], those with a more rapid (“hyperacute”) progression of liver injury to hepatic encephalopathy [9, 10], those with infection and/or the systemic inflammatory response syndrome (SIRS) [11, 12], and those requiring vasopressors or renal replacement therapy [6].

The treatment of cerebral edema in patients with ALF has not undergone major advancement since the early 1980s when studies from the King’s College in London suggested that the administration of mannitol decreased ICP in subjects with mild-to-moderate ICH [13]. These early observations consisted of only a few patients, however, and the favorable results did not apply to patients with severe ICH (e.g., >60 mmHg) or renal failure [14]. Another approach, the prophylactic administration of hypertonic saline (HTS) to achieve a serum sodium of 145–155 mM, has subsequently been shown to prevent the development of ICH in a single randomized, controlled study [15], but HTS has not been tested as a treatment of established ICH in patients with ALF. In patients with ICH despite osmotic therapy (mannitol and/or HTS), cerebral herniation is likely, and desperate measures may be considered, including the induction of barbiturate coma [8, 16] and the administration of indomethacin [17, 18] and/or paralytic agents. Even in patients who respond to osmotic therapy initially, relapse of ICH occurs frequently and requires further management to delay brain herniation.

Therapeutic hypothermia has become a commonly employed method to improve neurological recovery after cardiac arrest [19, 20], anoxia [21], and head trauma [22, 23], conditions in which cerebral edema contributes to brain injury. In experimental models of ALF, the induction of hypothermia also protects the brain [24–26], with beneficial effects on numerous physiological targets [27]. Based upon these experimental models, Jalan et al. [28] have pioneered the use of hypothermia in patients with ALF in various clinical situations (Table 1). A total of approximately 38 patients with ALF and uncontrolled ICH have been managed under hypothermic conditions, with each patient serving as his own control (i.e., in non-randomized studies). The first such report [29] consisted of seven patients with uncontrolled ICH, which was defined in this and subsequent studies as high grade hepatic encephalopathy (grades III/IV) and an ICP > 25 mmHg despite two boluses of mannitol (1 g/kg body weight over 20 min) and ultrafiltration (500 ml fluid removed). All were cooled to 32–33°C, for 8 h in patients not deemed OLT candidates, or 10–14 h in other patients, until they received a suitable graft. Mean ICP decreased from 45 to 16 mmHg after the institution of hypothermia; moreover, cerebral

blood flow decreased from 103 to 44 ml/100 g/min, and cerebral perfusion pressure increased from 45 to 70 mmHg. During hypothermia, there were no instances of relapse ICH, and the four patients deemed OLT candidates were successfully transplanted. In contrast, those deemed unsuitable OLT candidates all died after re-warming. These encouraging preliminary results were followed by a series of nine patients with ALF and uncontrolled ICH (same criteria as noted above), two of whom were included in the previous report [30]. Median ICP was reduced from 46 to 19 mmHg, and CBF from 111 to 56 mL/100 g/min, before and after the institution of hypothermia, respectively. Moreover, in six patients, hypothermia rapidly re-established CBF autoregulation and reactivity to carbon dioxide, which were defective under normothermic conditions.

ICH also represents a significant problem during OLT for ALF, even in some patients who do not exhibit an elevated ICP prior to OLT. Specifically, spikes in ICP and CBF occur during dissection of the native liver and after reperfusion of the liver allograft [31]. In a series of five patients with uncontrolled ICH (same criteria), Jalan et al. [31] have also shown that hypothermia (median 33.4°C) completely prevented such ICP spikes during these critical phases of OLT. Finally, Jalan et al. [32] have also used hypothermia (32–33°C) to bridge patients with ALF and uncontrolled ICH to OLT (Table 2). After the institution of hypothermia, all of 14 patients promptly normalized ICP (mean 36.6 before and 16.3 mmHg 4 h after hypothermia, respectively), and maintained similar levels of ICP until OLT for up to 118 h of cooling. Several patients required subsequent boluses of mannitol for transient ICH, and one died of cerebral herniation, but 13/14 subjects were successfully bridged to OLT.

These seminal observations, as well as a large body of supportive data from experimental animal models of ALF [24–26, 33], provide the rationale for a randomized, controlled trial of hypothermia in humans with ALF.

Toward a Randomized, Controlled Study of Hypothermia in ALF

Randomized clinical trials in patients with ALF are extremely difficult to perform for several reasons. First, ALF is not a uniform disease but a clinical syndrome with numerous etiologies and a natural history peculiar to each etiology; thus, the inclusion of patients with ALF of all etiologies into a trial is likely to result in uninterpretable results because of patient heterogeneity. Second, ALF is (fortunately) rare, and even the busiest liver transplant centers in the United States seldom care for more than 10 patients a year, requiring the participation of multiple centers in order to enroll sufficient patients within a

Table 1 Synopsis of patients with ALF who were treated with hypothermia in various clinical situations

Author (year)	APAP etiology (N)	ICP criterion (mmHg)	Temperature goal (°C)	Duration of cooling (h)	Reference
Jalan (1999)	6/7	>25	32–33	8–14	[29]
Jalan (2001)	7/9 ^a	>25	32–33.5	?	[30]
Jalan (2003)	5/5	>25	32–34	?	[31]
	7/5	<20	35	23–119	[48]
Jalan (2004)	13/14	>25	33 ± 0.5	10–118	[44]

APAP, acetaminophen; ICP, intracranial pressure

^a Two patients included in this series were also reported in [29]

Adapted from Vaquero and Butterworth [28]

Table 2 Effects of hypothermia (32–33°C) in patients with ALF and uncontrolled intracranial hypertension

	Pre-cooling	Hypothermia (4 h)	Hypothermia (10–24 h)
ICP (mmHg)	36.5	16.3	16.8
CBF (ml/100 g/min)	78.2	46.5	44.0
MAP (mmHg)	76.6	82.8	84.9

Note: Data represent means from 14 subjects with ICP > 25 mmHg despite two boluses of mannitol (1 g/kg body weight over 20 min) and removal of 500 ml of fluid by continuous veno-venous hemofiltration

ICP, intracranial pressure; CBF, cerebral blood flow; MAP, mean arterial pressure

Adapted from Jalan et al. [44]

reasonable time frame. Third, patients with ALF usually require many therapeutic maneuvers to treat dysfunction of nearly every organ system, all of which may have a significant impact on patient outcome, laboratory parameters of liver function, and ICP. As a corollary to this problem, there is no consensus protocol across centers regarding the management of such complications. Finally, the natural history of patients with ALF is frequently interrupted by OLT, the occurrence of which is based upon an educated guess regarding the likelihood of death without a transplant. Although many authors have proposed criteria to predict which patient will die without OLT (reviewed in [34]), no scheme has adequate predictive accuracy. Furthermore, the decision to proceed with OLT is based upon many non-medical factors, such as psychosocial and insurance issues. Thus, trials of ALF with survival and/or OLT as primary endpoints are inherently flawed.

The design of a trial of hypothermia in ALF must, therefore, address these and many other problems at the outset, including the identification of an appropriate study population, agreement on a common management protocol, and the definition of a primary endpoint to serve as a surrogate for outcomes in order to minimize the impact of OLT.

Identification of the Study Population

Based upon the above considerations, the optimal study candidates for a randomized, controlled trial of hypothermia in ALF would have the following characteristics:

1. They would be as clinically uniform as possible. Of all of the etiologies of ALF, patients with APAP overdose have the most characteristic clinical course, with rapid-onset hepatic encephalopathy after the ingestion of the drug [10, 35], and the beginning of spontaneous recovery of hepatic function, if it occurs, within 72 h [36–38]. Furthermore, the majority of patients with ALF due to APAP overdose recover spontaneously (~65%), and only a small minority undergo OLT (<10%) [39], which minimizes the problems of interpreting outcome data noted above.
2. They would be encountered frequently enough to ensure adequate patient accrual. Again, APAP overdose is by far the most common etiology of ALF in the United States [2] and in Western Europe [40], nearly 50%.
3. They would be at highest risk of developing cerebral edema. Although patients with ALF due to APAP overdose have the best prognosis without OLT, they paradoxically develop cerebral edema most frequently [9, 10]. As noted above, other risk factors for developing cerebral edema include high grade hepatic encephalopathy (grades 3–4) and high arterial ammonia concentrations (≥ 150 – 200 μM) [5, 6, 9].

Accordingly, the ideal study population for a trial of hypothermia in ALF would consist of patients with APAP overdose with high grade hepatic encephalopathy. Inclusion of patients with arterial ammonia ≥ 100 μM would also identify the highest risk population for ICH [6].

Primary Endpoint of a Study

In the current organ allocation systems in the United States and many nations in Western Europe, patients with ALF

are awarded highest priority for OLT (above patients with cirrhosis) as soon as they are placed on the waiting list. Consequently, the management and managers of wait-listed patients changes, introducing new variables into a randomized trial. As noted above, transplant also interrupts the natural history of the patient with ALF. Therefore, outcomes such as overall survival and rates of OLT in a hypothermia trial are not ideal primary endpoints despite their obvious importance as measures of efficacy.

Although ICH represents a reasonable alternate primary endpoint, the measurement of ICP introduces other problems. First, ICP monitors would be required in all study candidates. ICP monitor placement remains a controversial practice even in major transplant centers because they have not been shown to improve outcome in patients with ALF [41]. In addition, since ICP monitor placement carries a small but definite risk of intracranial bleeding and death [41, 42], a high likelihood of benefit must be demanded in order for the risk to be deemed ethical. For example, many liver transplant centers insert ICP monitors only in OLT candidates, with the belief that such monitoring serves to improve patient management as a bridge to transplant, but do not place monitors in non-transplant candidates. Furthermore, technical aspects of ICP monitor insertion in patients with ALF lack consensus between centers, such as intracranial location and the type of monitor employed [41]. Finally, ICP monitors malfunction frequently, require re-zeroing to maintain accurate readings, depend upon operator (nursing) experience, and must be validated for every reading in order to avoid collecting spurious data.

Despite these shortcomings, high ICP seems a rational primary endpoint of a study of hypothermia in patients with ALF at high risk of cerebral edema. Two uses of hypothermia should be examined: the effect of hypothermia on the *prevention* of ICH in patients with normal ICP on monitor placement (“prophylactic hypothermia”) and the effect of hypothermia on the *treatment* of ICH in patients with elevated ICP on monitor insertion. Most authorities would agree that an ICP of ≥ 25 mmHg indicates ICH in patients with ALF and the urgent need for intervention [13].

General Management

Patients with APAP-induced ALF must be treated according to the highest standards of medical care apart from their participation in a hypothermia trial. Specifically, intravenous NAC must be immediately administered on recognition of the diagnosis, and progression to high grade hepatic encephalopathy should prompt sedation and analgesia for urgent endotracheal intubation. Consultation with a neurosurgeon or other neurointensivist for insertion of an

ICP monitor, correction of the bleeding diathesis for ICP monitor placement, and activation of the OLT evaluation process (if appropriate) must be undertaken before consideration of administering hypothermia [34].

Administration of Temperature Control

In desperately ill patients with ALF, every detail of the administration of hypothermia requires careful consideration to avoid harm and maximize benefit in the absence of guidelines in the published literature.

How Should Subjects be Cooled?

In patients with ALF and ICH, the available literature suggests that hypothermia should be applied rapidly to achieve maximal benefit on ICP. In non-ALF populations, endovascular devices generally achieve goal temperatures more quickly than externally applied devices such as cooling blankets or jackets, and have the added benefit of monitoring core temperature from the same catheter [43]. ALF patients, however, differ from those with traumatic brain injury or cardiac arrest, in that they exhibit marked cutaneous vasodilation, allowing for extremely efficient heat exchange from external cooling devices. Indeed, preliminary studies in ALF patients show the achievement of goal temperature using cooling blankets within 1 h [31, 44]. Other considerations, such as the bleeding diathesis and high risk of infection in ALF patients, also suggest that external rather than endovascular devices may provide a safer mode of applying hypothermia.

How Cool Should Patients be Cooled?

As outlined in Table 1, most of the preliminary studies of hypothermia in patients with ALF have applied core temperatures of 32–33°C [29–31, 44], similar to studies in other disease states [22, 45]. Adverse effects of hypothermia, particularly infection and cardiac dysrhythmias, occur with core temperatures of $\leq 30^\circ\text{C}$ (Table 3) [46], and overshoot hypothermia to these levels must be strictly avoided. Concerns have also been raised regarding the potential adverse effect of deeper hypothermia on hepatic regeneration [47]. These considerations must be balanced, however, by the desire to apply an adequate level of hypothermia to observe a benefit on ICP and neurological recovery after ALF. Unfortunately, no dose–response analyses exist in patients with ALF.

Table 3 Adverse effects of hypothermia in non-ALF patients and proposed management in a randomized trial of hypothermia in patients with ALF

Function/System	Adverse effect	Associated °C	Prophylaxis/Management
CV	Arrhythmias	≤30	Prevent overshoot
Immune	WBC dysfunction/infection	≤33	Prophylactic antibiotics
Heme/Coag	Platelet dysfunction/coagulopathy	≤35	Gastric acid suppression
Renal	Diuresis/electrolyte depletion	≤35	Monitoring and repletion
GI	Hyperamylasemia	≤35	May not indicate pancreatitis
Metabolic	Hyperglycemia/drug metabolism	≤35	Short-acting insulin/dose adjustments

CV, cardiovascular system; Heme/Coag, hematologic-coagulation system; GI, gastrointestinal system

Adapted from Polderman [46]

How Long Should Patients be Cooled?

As noted in the preliminary studies above, patients with ALF have been subjected to hypothermia for up to about 5 days without adverse effects [44, 48]. Generally, the longer a patient is kept hypothermic, the greater the risk of adverse effects, in particular infection, such that it would seem undesirable to leave a patient hypothermic for long periods of time unless a clear goal, such as OLT, were imminent. This concern assumes more importance in patients who are not OLT candidates. As noted above, restoration of hepatic function (regeneration) usually occurs more rapidly in ALF due to APAP overdose, usually within 72 h, compared to ALF due to other etiologies. Therefore, 72 h represents a reasonable goal for assessing the efficacy of hypothermia on ICP in patients with ALF in non-OLT candidates, while longer periods might be reasonable in transplant wait-listed subjects.

How Fast Should Hypothermic Patients be Re-warmed?

Re-warming patients after therapeutic hypothermia risks several adverse events which may be particularly dangerous in patients with ALF. In addition to exacerbating electrolyte abnormalities, at times a dramatic problem in the ALF patient, re-warming also vasodilates hypothermic patients [46]. As above, since the ALF patient is already systemically vasodilated, further decrements in mean arterial pressure risks a critical drop in cerebral perfusion pressure (CPP) and cerebral ischemia. Scant literature exists regarding the rate of safe re-warming to minimize this risk. In the traumatic brain injury literature, re-warming rates of between 1°C/h and 1°C/day have been reported [22, 45, 49], and most of the preliminary reports of hypothermia in ALF patients have not included details of the rate of re-warming. Consequently, it would seem prudent to re-warm patients with ALF slowly, perhaps 1°C every 12 h.

Should Patients Randomized to be Managed Under Normothermic Conditions be Actively Warmed?

Patients with ALF frequently experience spontaneous core temperatures of 34–36°C due to cutaneous vasodilation and iatrogenic maneuvers, particularly renal replacement therapy. Indeed, the potential benefit of hypothermia may be diluted in a trial where the normothermic control group also becomes hypothermic. Active warming of patients with ALF assigned to the normothermic group raises ethical concerns, since the hypothesis of the study, and a convincing body of preliminary data, suggests that hypothermia will improve cerebral edema. Furthermore, fever adversely affects ICP in ALF patients [50] and in those with other neurological conditions [51], intensifying concern that actively warming a patient with ICH may do harm. A reasonable compromise might include maintaining patients in the normothermic group at a set low-normal temperature such as 36–37°C using the same thermal control device as those randomized to receive hypothermia.

Other Problems to be Considered

Definitions of Treatment Failure and Improvement

Considering the preliminary data supporting the efficacy of hypothermia in lowering ICP in refractory ICH, subjects randomized to the normothermia arm who are deemed medical treatment failures should be considered for cross-over hypothermia. Few would argue that the definition of uncontrolled ICH as proposed above by Jalan represents a high risk of cerebral herniation and/or poor neurological recovery after OLT. However, others would also advocate the administration of hypertonic saline to a serum sodium of up to 155 mM [15], the administration of paralytic agents and deeper sedation including barbiturates [8, 16], and/or intravenous indomethacin [18] before labeling ICH truly uncontrolled. An ICP ≥25 mmHg after all such

desperate measures have been exhausted indicates that cerebral herniation is imminent, a strong argument in favor of crossing-over normothermic patients to receive hypothermia.

Conversely, recovery of hepatic function requires definition in order to begin re-warming to avoid potential adverse effects of hypothermia. In ALF patients with normal ICP, the degree of hepatic function required to prevent ICH after re-warming, and the quantification of this recovery, remains poorly defined. Decreases in arterial ammonia to less than 100 μ M, decreases in INR to <1.5, and an improvement in factor V levels to >30% of normal with a trend of improvement over 72 h [38] all indicate restoration of hepatic function and might be indications for re-warming, with the understanding that rebound ICH may still occur [29].

Problems with Recruitment and Data Analysis

Unfortunately, calculating a sample size to ensure an adequately powered trial can only be based upon imprecise data, since the prevalence and natural history of ICH in ALF patients with high-grade hepatic encephalopathy from APAP overdose has not been well defined. Enrollment will also be a concern because of the scarcity of patients meeting these specific entry criteria, and multi-center and possibly multi-national participation will be required. A detailed ALF management protocol addressing every aspect of the intensive of these complicated patients, such as that recently published by the US ALF Study Group [34], must be in place. Furthermore, mechanisms to ensure protocol adherence must be agreed upon, as protocol deviation has been incriminated in the failure of one large study of hypothermia in traumatic brain injury patients [52]. Interpretation of data and outcomes will also be complicated by the lack of investigator and care-giver blinding, since patients randomized to receive hypothermia are likely to be monitored and treated more intensively than those managed under normothermic conditions, a source of bias.

Finally, the delivery of hypothermia in ALF patients must be intensely scrutinized for adverse effects. The available data suggest that hypothermia to 32°C is well tolerated by ALF patients [29–31, 44]. However, as shown in Table 3 in non-ALF patients, hypothermia poses major safety concerns affecting practically all organ systems and functions [46]. Furthermore, differentiating adverse effects of hypothermia from the complications of ALF itself will be difficult as they are strikingly similar [34, 46]. Mechanisms to study the effects of hypothermia on hepatic regeneration must also be addressed [47].

Conclusions

The pioneering work of Jalan and colleagues, and many other basic scientists, strongly argues that the time is right for a randomized, controlled trial of hypothermia in patients with ALF and advanced hepatic encephalopathy. To quote the most renowned investigator in the field, Professor Roger Williams, “Randomized clinical trials in acute liver failure are a nightmare to do...” The discussion above would support this statement, but would also support the effort as very likely to improve the management of patients with ALF.

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