Research Article

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A multicentre randomized controlled trial of moderate hypothermia to prevent intracranial hypertension in acute liver failure

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See Editorial, pages 240–242

Background & Aims: Animal models and human case series of acute liver failure (ALF) suggest moderate hypothermia (MH) to have protective effects against cerebral oedema (CO) development and intracranial hypertension (ICH). However, the optimum temperature for patient management is unknown. In a prospective randomized controlled trial we investigated if maintenance of MH prevented development of ICH in ALF patients at high risk of the complication.

Methods: Patients with ALF, high-grade encephalopathy and intracranial pressure (ICP) monitoring in specialist intensive care units were randomized by sealed envelope to targeted temperature management (TTM) groups of 34 °C (MH) or 36 °C (control) for a period of 72 h. Investigators were not blinded to group assignment. The primary outcome was a sustained elevation in ICP >25 mmHg, with secondary outcomes the occurrence of predefined serious adverse effects, magnitude of ICP elevations and cerebral and all-cause hospital mortality (with or without transplantation).

Results: Forty-six patients were randomized, of whom forty-three were studied. There was no significant difference between the TTM groups in the primary outcome during the study period (35% *vs.* 27%, $p = 0.56$), for the MH (n = 17) or control (n = 26) groups respectively, relative risk 1.31 (95% CI 0.53–3.2). Groups had similar incidence of adverse events and overall mortality (41% *vs.* 46%, $p = 0.75$).

Conclusions: In patients with ALF at high risk of ICH, MH at 33–34 °C did not confer a benefit above management at 36 °C in prevention of ICH or in overall survival. This study did not confirm advantage of its prophylactic use. (ISRCTN registration number 74268282; no funding.)

Lay summary: Studies in animals with acute liver failure (ALF) have suggested that cooling (hypothermia) could prevent or limit the development of brain swelling, a dangerous complication of the condition. There is limited data on its effects in humans. In a randomized controlled trial in severely ill patients with ALF we compared the effects of different temperatures and found no benefit on improving survival or preventing brain swelling by controlling temperature at 33–34 °C against 36 °C.

Keywords: Hypothermia; Acute liver failure; Encephalopathy; Cerebral oedema; Transplantation; Randomized controlled trial.

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Abbreviations: ALF, acute liver failure; ELT, emergency liver transplantation; HE, hepatic encephalopathy; CO, cerebral oedema; ICP, intracranial pressure; ICH, intracranial hypertension; TTM, targeted temperature management; MH, moderate hypothermia; RCT, randomized controlled trial; ICU, intensive care unit; INR, international normalised ratio; RRT, renal replacement therapy; CVVHF, continuous veno-venous hemofiltration; NAC, N-acetyl cysteine; CPP, cerebral perfusion pressure; MOF, multiple organ failure; DILI, drug-induced liver injury; KCC, Kings College criteria; SOFA, sequential organ failure assessment score; WBC, white blood cell count; AST, aspartate transaminase; HR, heart rate; MAP, mean arterial pressure.

Introduction

Acute liver failure (ALF) is a rare critical illness that continues to have a high mortality, despite advances in supportive intensive care management and the utilization of emergency liver transplantation (ELT). It is characterized by an acute liver injury resulting from a wide variety of hepatic insults in the absence of pre-existing liver disease, and complicated by the development of hepatic encephalopathy (HE). In addition, patients often develop simultaneous multiple organ systems failure [1].

In severe cases, HE may progress with the development of cerebral oedema (CO), elevated intracranial pressure (ICP) and intracranial hypertension (ICH), a feared complication and important cause of death. Approaches to the intensive care management of patients with ALF therefore include a package of neuroprotective measures designed to prevent its development or ameliorate its severity [1,2]. Targeted temperature management (TTM) and the induction of moderate hypothermia (MH) may be employed as part of this [3]. Animal models suggest it to have cerebral and systemic effects of particular benefit in this setting, preventing the development of CO and controlling refractory elevation of ICP when it has evolved [3–6]. The decrease in cerebral metabolic activity seen with MH may lower the pathological metabolism of ammonia, the likely principal neurotoxin in the development of CO, and attenuate local and systemic inflammation, thought to have an important permissive effect [3,5,6]. Human case series suggest that MH may be effective in controlling otherwise refractory elevations in ICP, beneficially modulate local and systemic inflammatory status and associated with increased hemodynamic stability and improved cerebral perfusion [7–9].

However there are no human trial data to suggest an optimum temperature for patient management, or whether MH is effective in the preventing development of elevated ICP. Concerns also exist in relation to the induction by MH of clinically significant adverse effects [3,10]. Studies in patients with severe neurotrauma suggest that ICP may be lowered by application of MH, but fail to demonstrate consistent evidence of improved survival [11]. Recent data on the use of TTM in patients who have suffered out of hospital cardiac arrest also showed no mortality benefit associated with hypothermia [12–14]. In the setting of human ALF adverse events might include worsening of already significant coagulopathy, impaired hepatic regeneration, and of increased susceptibility to infection – important as a contraindication to ELT and a key cause of death [10,15,16].

Therefore, there is a clear need to determine the efficacy or otherwise of MH in ALF patients at high risk of developing ICH, and its impact on development and severity of ICH and safety profile. ALF is a uniquely difficult condition in which to perform randomized controlled trials. This relates to its rarity, severity, heterogeneity and the rapidity of illness progression, which make participant recruitment and study challenging. The use of ELT further complicates interpretation as the duration of any intervention may be truncated and treatment effects difficult to ascertain. Consequently, few RCT of any sort have been performed in patients with ALF, and when undertaken may take many years to enrol [17,18].

Here, we performed a pragmatic multicentre randomized controlled trial of TTM in ALF, aiming to study patients at high risk of CO and investigate whether the onset of clinically significant elevations of ICP might be prevented or delayed by the use of induced MH.

Patients and methods

Patients, trial setting and design

This randomized controlled trial recruited patients with ALF in 3 specialist intensive care units (ICU) in the United Kingdom and Denmark and was approved by the ethics committees of each country and institution. The trial was registered with ISRCTN (ISRCTN74268282).

ALF was defined as: (1) an international normalized ratio (INR) of $\geqslant$1.5; (2) absence of a previous history and clinical/radiologic findings of liver disease; (3) illness $\leqslant$26 weeks duration and (4) overt encephalopathy of grade $\geqslant$3. We screened consecutive patients of 18 years or older with ALF who had developed HE of grade $\geqslant$3 who had been intubated, sedated and mechanically ventilated and who were considered at high risk of ICH such that the treating clinician had inserted a Camino® ICP monitor. Informed assent was then obtained from the next-of-kin of all participants, and consent confirmed in those patients who recovered; inclusion in the trial was within 12 h of insertion of the ICP monitor. Exclusion criteria included pregnancy, evidence of brain stem death, ongoing or suspected haemorrhage, suspected or microbiologically confirmed severe sepsis such that MH induction was considered inappropriate, and no or withdrawn consent.

Supportive care

Standard medical care applied has been detailed elsewhere and a common approach was taken in all centres [1]. In brief, guided restoration of circulating volume was commenced immediately on admission and supported through use of invasive hemodynamic monitoring. Norepinephrine was the primary vasopressor used and dobutamine the primary inotropic agent with adjunctive use of intravenous low dose hydrocortisone and vasopressin. Renal replacement therapy (RRT) was undertaken using continuous veno-venous hemofiltration (CVVHF). Indications for its use included not only those standard for patients with acute kidney injury but also anuria, relative oliguria, metabolic stabilization, control of acidosis and hyper-ammonaemia. Hypertonic saline was infused to maintain serum sodium at 140–150 mM/L. Sedation utilized fentanyl, and propofol infusions and neuromuscular blockade was not routinely undertaken. Intracranial pressure monitors were inserted at the discretion of the treating clinician on the basis of clinical signs of ICH and /or clinical risk factors for its development [19,20].

Mean arterial pressure was maintained at >65 mmHg, cerebral perfusion pressure (CPP) was managed at the discretion of the clinician dependent upon the presence or absence of autoregulation. Arterial pCO_2 was targeted at 4–5 kPa.

Treatment for ICH crises as defined by sustained elevation of ICP >25 mmHg was with sequential use of sedation bolus whilst maintaining adequate perfusion pressure then with bolus intravenous mannitol 20% (0.5 g/kg) or hypertonic saline (30% 20 mls); with use of thiopentone and/or intravenous indomethacin in refractory cases. Intravenous N-acetyl cysteine (NAC) was administered to all patients with an infusion of 150 mg/kg/24 h for a maximum of 5 days or until the INR was <2. Intravenous broad-spectrum antibiotics were administered to all patients in the trial. In those patients transplanted, immunosuppression was with tacrolimus and corticosteroids.

Randomization and trial intervention

After confirmation of eligibility and assent, patients were randomly assigned to TTM groups with a target core body temperature of either 34 °C (MH) or 36 °C (Controls). Randomization was performed nationally, by sealed envelope and in blocks of varying size by country. The intervention period of 72 h commenced at the time of randomization; the treating clinicians were not blinded to the intervention.

Sedation and ventilation was mandated in all patients until the end of the intervention period but sedation targets and the drugs used to achieve targets were left to the discretion of the local clinicians. The goal was to achieve the assigned temperature as rapidly as possible with the use of surface temperature management devices (warming and cooling) and where present, control of blood temperature through continuous RRT extracorporeal circuits.

After the trial period, rewarming to 36–37 °C was commenced in both groups at the discretion of the treating physician and subsequent management was in accordance with standard medical practice including avoidance of fever (>37 °C). In those patients who underwent ELT rewarming was permitted prior to surgery if there was concern with bleeding risk, and following return to ICU the patient was managed with a temperature of 36–37 °C.

Outcomes

The primary outcome was a sustained elevation in ICP >25 mmHg for 5 min. Secondary outcomes included the occurrence of predefined serious adverse effects of thrombocytopenia, spontaneous haemorrhage, cardiac dysrhythmias, confirmed sepsis or acute pancreatitis. Other secondary outcomes considered included the absolute magnitude of ICP elevations and cerebral and all-cause mortality. Follow-up was to hospital discharge.