Research Article

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High-volume plasma exchange in patients with acute liver failure: An open randomised controlled trial

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See Editorial, pages 10–12

Background & Aims: Acute liver failure (ALF) often results in cardiovascular instability, renal failure, brain oedema and death either due to irreversible shock, cerebral herniation or development of multiple organ failure. High-volume plasma exchange (HVP), defined as exchange of 8–12 or 15% of ideal body weight with fresh frozen plasma in case series improves systemic, cerebral and splanchnic parameters.

Methods: In this prospective, randomised, controlled, multicentre trial we randomly assigned 182 patients with ALF to receive either standard medical therapy (SMT; 90 patients) or SMT plus HVP for three days (92 patients). The baseline characteristics of the groups were similar. The primary endpoint was liver transplantation-free survival during hospital stay. Secondary-endpoints included survival after liver transplantation with or without HVP with intention-to-treat analysis. A proof-of-principle study evaluating the effect of HVP on the immune cell function was also undertaken.

Results: For the entire patient population, overall hospital survival was 58.7% for patients treated with HVP *vs.* 47.8% for the control group (hazard ratio (HR), with stratification for liver transplantation: 0.56; 95% confidence interval (CI), 0.36–0.86; $p = 0.0083$). HVP prior to transplantation did not improve survival compared with patients who received SMT alone (CI 0.37 to 3.98; $p = 0.75$). The incidence of severe adverse events was similar in the two groups. Systemic inflammatory response syndrome (SIRS) and sequential organ failure assessment (SOFA) scores fell in the treated group compared to control group, over the study period ($p < 0.001$).

Conclusions: Treatment with HVP improves outcome in patients with ALF by increasing liver transplant-free survival. This is attributable to attenuation of innate immune activation and amelioration of multi-organ dysfunction.

Introduction

Acute liver injury is most often associated with discrete non-specific symptoms and mildly elevated liver function tests. In severe cases progressing to acute liver failure (ALF), the conscious level decreases, and brain oedema, hypoglycaemia, and extra hepatic organ failure evolves [1].

The exact pathophysiology for development of multi-organ dysfunction (MOF) in ALF remains elusive. There is an accumulation of various metabolites and toxins varying in size, distribution volume, lipophilicity, and protein binding [2,3]. Studies in ALF patients also indicate that a decreased hepatic capacity for synthesis of coagulation factors, complement, and lipoproteins may be of importance in the evolution of MOF. The importance of systemic inflammatory responses (SIRS) in the outcome in ALF has been established for over a decade, being associated with MOF, progression in encephalopathy and increased mortality [4–7]. Recent evidence indicates that following overwhelming hepatocyte death, there is the release of damage associated molecular patterns (DAMPS),

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Abbreviations: ALF, acute liver failure; ALT, alanine-aminotransferase; CI, confidence interval; CLIF, Chronic liver failure consortium; FiO2, fractional inspired oxygen; HR, hazard ratio; ICP, intracranial pressure; ITT, intention to treat; NH3, ammonia; LPS, lipopolysaccharide; PE, plasma exchange; RR, respiratory rate; IQR, interquartile range; SD, standard deviation; SMT, standard medical treatment; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure score.

e.g. DNA, histones, HMGB-1, trigger Toll-like receptor (TLR) dependent activation of innate immune cells, hepatic and systemic inflammatory responses [1,4].

Survival with medical management has increased over the last three decades but a significant mortality remains [2,3]. The management strategy of ALF patients is to restore and preserve vital organ function and mitigate or limit the progression of MOF until either spontaneous liver regeneration occurs or a suitable donor liver becomes available for emergency liver transplantation in those identified to be likely non-survivors [3,8,9]. In this context an effective liver assist procedure may improve survival for those with ALF deemed not appropriate for liver transplantation, despite poor prognostic criteria and/or providing greater stability whilst awaiting transplantation.

Any intervention that aims to replace the failing liver should secure metabolic and excretory functions, replace liver-derived proteins and peptides and attenuate the severity of any innate immune activation following acute hepatocyte injury [10].

Most studies of extracorporeal liver support have been based upon dialysis techniques assuming that ALF can be treated by a device that corrects blood's composition. Thus far, such procedures have been of limited success and currently no study has been able to demonstrate an improvement in survival in patients with ALF [11–13].

Plasma replacement or exchange therapy with fresh frozen plasma is an established therapy used for other immunologically-driven disorders [14]. Case series of high-volume plasma exchange (HVP) in patients with ALF have been shown to be safe [15,16], to decrease the severity of hepatic encephalopathy, decrease vasopressor requirements [17,18] and with a signal of accelerated hepatic nitrogen turnover [19,20].

The mechanism of action of therapeutic plasma exchange in ameliorating the course of various diseases is putative and pertains to the removal of plasma cytokines and adhesion molecules, replacement of plasma factors, and immune modulation. In this study we hypothesised that HVP would reduce mortality in patients with ALF by attenuating the development of MOF. The primary endpoint was transplant-free survival during the hospital stay. The secondary endpoint included survival after transplantation with or without HVP using an intention-to-treat analysis. In addition we performed a proof-of-principle study evaluating the effects of HVP on circulating immune cells and leucocyte subsets.

Patients and methods

This study was conducted in two parts. Study A: ALF patients randomised to standard medical treatment (SMT) and to SMT plus HVP. Study B: examined the effect of plasma obtained before and after the first HVP session from ALF patients on the circulating immune cell subsets innate and native immune system.

Study A

Trial design

The eligibility criteria were age greater than 18 years and a diagnosis of ALF with at least grade 2 hepatic encephalopathy [21]. All aetiologies including acute Wilson's disease, Budd-Chiari syndrome and acute presentation of autoimmune hepatitis (without clinical or radiological evidence of cirrhosis or chronic liver injury in the later two cohorts) were eligible for inclusion. Twenty-six patients were listed for liver transplantation (LTx) in the HVP treated group *vs.* 30 in the in the control group (NS). Before enrolment into the study, all patients had review of possible aetiological factors and clinical examination. A diagnostic ALF screen was secured incorporating serological tests, hepatitis serology, autoimmune markers, and microbiological cultures, in addition to ultrasound imaging and/or CT imaging as determined by the treating clinician.

Exclusion criteria included withdrawal of assent, alcoholic hepatitis, primary non-function of liver graft or graft dysfunction, any form of known chronic liver disease, known malignancies, liver resections with liver failure, hypoxic hepatitis and malignancy presenting as ALF. Patients with clinical suspicion of irreversible brain injury (fixed dilated pupils unresponsive to standard interventions) or brain death were excluded from enrolment.

The protocol was approved by the institutional review board or ethics committee at each centre alongside appropriate adherence to all applicable laws and regulations governing clinical research. Assent/consent for entry into the trial was obtained from the patienťs nominated representative.

Randomisation

Entry into the study was required within 24 h of the development of grade 2 encephalopathy. When a patient was identified as suitable for study entry, a research co-ordinator was telephoned in the co-ordinating centre (Copenhagen) and SMT or SMT plus HVP was defined from a pre-made randomization code that was blinded to the co-ordinator (transplant coordinating staff) and the investigators by using opaque envelopes.

Eligible and consented patients were randomly assigned, in a 1:1 ratio, to receive either SMT or SMT plus HVP with no block randomisation. The study was not blinded.

At entry to intensive care, at randomization, study entry and during the study period, patients were defined as fulfilling poor prognostic criteria based on the King's College Criteria [1–4]. Reasons for not being active on the urgent transplant list despite fulfilling poor prognostic criteria were documented.

Patients and methods

All patients were treated in three specialised liver intensive care units with SMT as outlined in the study protocol (ClinicalTrials Gov Number NCT00950508). Transfusion triggers were as per local guidelines, coagulation support using plasma was not routinely offered in the SMT group. Use of intravenous insulin, hypertonic dextrose and enteral feeding were all utilised to maintain euglycaemia.

Intubation and ventilation was undertaken for standard indications in addition to development of grade 3 encephalopathy, with infusion of sedation (propofol or midazolam and opiates) to facilitate effective ventilation. H2 antagonist or proton pump inhibitors, antibiotics and antifungal regimes followed local guidelines with microbiological input.

Advanced haemodynamic monitoring was undertaken, with clinical goals of euvolaemia with mean arterial pressure maintained at greater than 60 mmHg. First choice of pressor was norepinephrine, with dobutamine as first line inotrope. The use of dopamine, adrenaline and terlipressin were allowed as additional vasopressors.

N-Acetylcysteine, was given to all patients irrespective of aetiology [22] and given for a maximum of five days. The primary mode of renal replacement therapy was continuous haemofiltration. Intermittent haemodialysis was allowed only if the patient showed haemodynamically stability and there was no concern regarding cerebral deterioration or cerebral oedema. Anticoagulation of extracorporeal circuits followed local guidelines with use of low dose heparin, epoprostenol or nothing. Cerebral CT scan was not required before enrolment into the study.

Intracranial pressure (ICP) monitoring was instituted if the attending clinician felt it was indicated. An episode with a sustained increase in ICP >20 mmHg for more than 5 min was defined as intracranial hypertension.

Plasma exchange procedure

The volume of HVP exchanged was stipulated as 15% of ideal body weight (representing 8–12 L per day per procedure); patient plasma was removed at a rate of 1–2 L per hour with replacement with fresh frozen plasma in equivalent volume. The HVP procedure was undertaken on three consecutive days but with no fixed time interval between each treatment.

Data collection

Physiological and laboratory parameters were collected prospectively during a 12 year period (1998–2010), allowing retrospective calculation of both sequential organ failure assessment score (SOFA) score [23] and CLIF-SOFA score [24] and SIRS parameters [25]. Outcome was defined as survival to hospital discharge or death; data was collected on a predefined CRF.

Statistics

The sample size calculation was based upon retrospective observations of mortality of patients with ALF. Assuming a 20% improvement in survival with the intervention, for a significance level of rate of 5% with a beta-value of 20% we calculated that 182 patients should be enrolled. Two predefined interim analyses were planned at 60 and 120 patients examining safety and futility endpoints.