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Therapeutic plasma exchange: A prospective randomized trial to evaluate 2 strategies in patients with liver failure

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ABSTRACT

Objective: To compare two means of performing therapeutic plasma exchange (TPE) in patients with liver failure.
Method: This open-label monocentric randomized trial, conducted in a single prestigious general healthcare facility, recruited liver failure patients with an indication to receive artificial liver support therapy for TPE. All patients underwent TPE procedures and were administered in a random sequence: heparin-free or systemic heparinization with unfractionated heparin. The primary endpoint was completion of TPE sessions, and the secondary endpoints included the safety and efficacy.
Results: In the period of the studying, there were 164 patients being recruited in and underwent total of 398 randomized TPEs: 168 with unfractionated heparin and 230 with heparin-free. In unfractionated heparin group, there were 3 cases (1.79%) being interrupted due to uncontrollable intraoperative pulmonary hemorrhages and gastrointestinal bleeding. In heparin-free group, 228 (99.13%) were completed successfully and 2 of them (0.87%) were switched from heparin-free to unfractionated heparin eventually. No significant differences were found between the two groups for either RRs or IRs ($P > 0.05$).
Conclusion: Heparin-free regimen is feasible and safer than systemic heparinization with unfractionated heparin in the process of TPEs in patients with liver failure.

1. Introduction

Liver failure is a common medical ailment characterized by encephalopathy and impaired liver synthetic function. In China, the syndrome is mainly caused by hepatitis B infection, followed by conditions such as autoimmune hepatitis, drug-induced liver injuries, alcohol-induced liver injuries, pregnancy-related liver failure. The lack of liver detoxification leads to a rapid increase in soluble and lipid soluble toxin concentrations, which results in a vicious cycle, i.e., toxins further aggravate liver failure, which leads to increased production of toxins. Thus, patients with acute, sub acute, acute-on-chronic or chronic liver failure show a poor prognosis and a mortality rate of 60–80%, receiving conservative treatment [1,2]. The therapeutic strategies for liver failure differ between China, Europe and the United States. Cadaveric transplantation is considered as the first-line therapy for liver failure in Europe and the United States [3], while in China, artificial liver support, consisting of various blood purification techniques, especially therapeutic plasma exchange (TPE), is usually provided first to patients with liver failure [4]. During the process of TPE, the patient's plasma with hepatic toxins is replaced by equally volume of normal donor plasma, which normally contains a lot of clotting factors. TPE has been found to be useful in the management of individuals with drug-induced, pregnancy-related, autoimmune, hyperthyroidism-associated and fulminate liver failure [5–15], but TPE-related bleeding complications are notable, this is because patients with liver injuries have a balanced but brittle coagulation system, and the heparin, which is common administered to avoid clotting in the extracorporeal blood circuit during the TPE procedure [16–18], of course plays the role of trigger. Heparin can exacerbate coagulation disorders and aggravate bleeding in liver failure patients through inhibition of several activated clotting factors (especially factors IIa and Xa) via its activation of antithrombin III. Thus, heparin-free TPE (HF-TPE) in liver failure may decrease the risk of bleeding. However, no clear data on the efficacy and safety of HF-TPE in liver failure are available in the literature. Therefore, the aims of this study were (A) to investigate the feasibility of HF-TPE and (B) to compare the efficacy and safety of means with heparin-

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free versus unfractionated heparin regimen when performing TPE in patients with liver failure.

2. Materials and methods

2.1. Patients, study design and sample selection

This was a prospective randomized study being performed at a single prestigious general health care center (Xiangya Hospital Central South University, Changsha City in China). The study was limited to adult patients (age over 18 years) with liver failure who had been admitted to this clinical unit. Diagnostic criteria for liver failure was based on medical history, clinical manifestation and auxiliary examination, as defined by the guideline for diagnosis and treatment of liver failure revised by the Chinese Medical Association (CMA) in 2012 [4], which were established by the Liver Failure and Artificial Liver Group, Chinese Society of Infectious Diseases, CMA. Another inclusion criterion was that the patient was scheduled to receive TPE. The third was he or she was voluntary. Exclusion criteria were those with: active hemorrhage before TPE treatment, heart dysfunction, blood disorders, or heparin or other anticoagulant treatment in the past 15 days. We used a cluster sampling method to obtain the total sample from July 2012 to July 2014. Patients fulfilling all inclusion and exclusion criteria were recruited in this open-label trial and randomly divided into heparin TPE (H-TPE) and HF-TPE groups, the random allocation was generated by computer in an independent department and send to us by fax. The study was approved by the ethics committee of the Central South University Hospital prior to patient recruitment. Prior to treatment, written informed consent was obtained from each subject, or in the presence of hepatic encephalopathy, from their next of kin.

2.2. Procedures

Blood purification access was by double-lumen catheter of the femoral vein, and TPE was performed with a therapeutic apparatus and plasma separator EC-4A (Kuraray Co., Tokyo, Japan). The extracorporeal circulation conduct of blood purification apparatus was full filled with heparinized saline (1000 ml saline with 3125 U unfractionated heparin) for 30 min before TPE procedure. The blood of the patients was drew out and passed through a plasma separation instrument (PE 8900-a, Asahi Kasei, Japan) with an initial flow rate of 50–70 ml/min and a maximal flow rate of 120–130 ml/min. Patient's plasma components were separated out when passing the selective plasma separator and afterwards were routed into the waste bag and discarded. In the meantime, equally volume of human fresh-frozen plasma was infused into patient's circulatory system with those blood cells, which were separated out when passing the selective plasma separator, via the double-lumen catheter of the femoral vein. The plasma separation speed was 20–40 ml/min, and the treatment lasted for 1.5–2 h. Using the equation PV = (1 − HCT) (b + cW), we used 1.2–1.3 plasma volumes (PV = plasma volume; HCT = hematocrit; W = weight; b = constant, 1530 for males and 864 for females; c = constant, 41 men and 47.2 for women) [19].

In the HF-TPE group, anticoagulants were not used throughout the entire treatment, and the pre-washed heparin saline in the extracorporeal circulation conduct was discarded and did not infuse into patient's circulatory system as well. The circulation loop and plasma separator were observed closely, and evidence of coagulation would trigger the administrating of anticoagulant or early termination of the trial.

In H-TPE group, the pre-washed heparin saline in the extracorporeal circulation conduct was discarded as well, but as usual, these patients received a bolus of 2500 IU unfractionated heparin at the beginning of the blood purification procedure and then followed by a maintenance unfractionated heparin infusion of 50 IU/h. At the end of TPEs, the patient was given intravenous protamine at a 2:1 ratio. Dexamethasone or other immunosuppressive agents were not required for allergic prophylaxis in either group.

2.3. Outcomes and measurements

The primary endpoint was the percentage of completing TPEs successfully. Causes of preterm interruption of TPEs were in recorded in detail. The secondary endpoints included the safety and efficacy. A semi-quantitative dialyzer clotting score were used to assess the extracorporeal circuit clotting [20]. Coagulation indicators such as prothrombin time activity (PTA) percentage, activated partial thromboplastin time (APTT), international normalized ratio (INR), and fibrinogen were detected pre- and post-procedure every single TPE. Treatment efficacy was defined as bilirubin (total) reduction ratios (RR), and albumin increase ratio (IR), which were calculated as RR = (Cpre − Cpost)/Cpre and IR = (Cpost − Cpre)/Cpre, respectively.

2.4. Statistics

Data are expressed as mean (minimum, maximum) or percentage. Bleeding and clotting events due to TPE were estimated by Pearson chi-square test. Analysis of variance of repeated measures was used for the inter-group and intra-group trends comparison of biochemical, coagulation parameters and blood cell counts, Independent-samples *T*-test for equality of means was used for the pre- and post-procedure difference value of biochemical, coagulation parameters and blood cell counts for inter-group. Two-tailed 95%CIs were used for all analyses, a P value ≤ 0.05 was chosen to indicate statistical significance. All statistics were performed using SPSS PASW Statistics, version 18.

3. Results

3.1. Patient characteristics and treatment allocations

During the period from July 2012 and July 2014, 186 patients on liver failure fulfilling all inclusion and exclusion criteria were considered for potential enrolment. 22 patients declined to be enrolled. Eventually, a total of 164 patients (148 men, 16 women; median age 45 years) agreed, were included in the study, and underwent randomization, and a total of 398 TPEs was performed: 168 with unfractionated heparin and 230 with heparin-free. Two groups' baseline characteristics are presented in Table 1. Approximately two-third of the cases was suffering from hepatitis B and acute-on-chronic liver failure. The study included two being switched from heparin-free to unfractionated heparin anticoagulation. The distribution of gender, age, etiology and classification did not differ between the two groups detailed in Table 1.

3.2. Completion of treatment and the change of coagulation index in H-TPE group

Of the 168 sessions, 165 (98.21%) were completed successfully, 2 (1.19%) were interrupted due to uncontrollable intraoperative pulmonary hemorrhages and gastrointestinal bleeding, and one case (0.6%) occurred gastrointestinal bleeding in 6 h after the treatment. Three cases with organ hemorrhage above resulted in hypotension, hemorrhagic shock and eventually coma before death within 12 h. Besides, there were 3 cases with vascular access site bleeding when the double-lumen catheter of the femoral vein had been removed for 6 h, and bleeding volume reached 100 ml per cases in

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