Plasma exchange-centered artificial liver support system in hepatitis B virus-related acute-on-chronic liver failure: a nationwide prospective multicenter study in China

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BACKGROUND: Plasma exchange (PE)-centered artificial liver support system reduced the high mortality rate of hepatitis B virus (HBV)-related acute-on-chronic liver failure (ACLF). But the data were diverse in different medical centers. The present prospective nationwide study was to evaluate the effects of PE on patients with HBV-ACLF at different stages.

METHODS: From December 2009 to December 2011, we evaluated 250 patients at different stages of HBV-ACLF from 10 major medical centers in China. All the laboratory parameters were collected at admission, before and after PE.

RESULTS: Among the 250 patients who underwent 661 rounds of PE, one-month survival rate was 61.6%; 141 (56.4%) showed improvement after PE. Variables such as age (*P*=0.000), levels of total bilirubin (TB, *P*=0.000), direct bilirubin (*P*=0.000), total triglycerides (*P*=0.000), low-density lipoprotein (*P*=0.022), Na^+ (*P*=0.014), Cl^- (*P*=0.038), creatinine (Cr, *P*=0.007), fibrinogen (*P*=0.000), prothrombin time (PT, *P*=0.000), white blood cell (*P*=0.000), platelet (*P*=0.003) and MELD (*P*=0.000) were significantly related to prognosis. Multivariate logistic regression analysis showed that age, disease stage, TB, Cr and PT levels were independent risk factors of mortality among HBV-ACLF patients.

CONCLUSIONS: PE can improve the clinical outcome of patients with HBV-ACLF. Levels of TB, Cr and PT, age and disease stage help to predict prognosis.

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KEY WORDS: liver failure; artificial liver support; plasma exchange; acute-on-chronic liver failure

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Introduction

Hepatitis B virus (HBV) has a high prevalence rate worldwide; an estimated more than two billion people were infected and approximately 400 million individuals had chronic HBV infection. In China, acute exacerbation of chronic HBV is the most

common cause of acute-on-chronic liver failure (ACLF); the main etiologies in Western countries are drugs, alcohol, and hepatitis C.[1] Although the liver is scarred and distorted in compensated stage, it still performs many important functions such as synthesis, detoxification, excretion, biotransformation, etc. When insulted, the hepatocytes show necrosis underlying the original pathologic damage and that liver failure occurs. Patients with liver failure manifest as coagulopathy, jaundice, hepatic encephalopathy (HE), and ascites. Despite recent progress in antiviral therapy, liver failure remains a therapeutic challenge with a high mortality rate.[2, 3] Liver transplantation, the only effective treatment, is hampered by the shortage of organs[4, 5] and the high frequency of concomitant conditions that contraindicate the procedure. Artificial liver support system (ALSS), which originated from concept of hepatocyte regeneration, is an effective alternative treatment for liver failure. ALSS temporarily eliminates toxic substances and replaces the failed liver with an environment for the regeneration of hepatocytes or an environment that enables the patients to wait for liver transplantation.[6]

Many types of extracorporeal blood purification systems, including plasma exchange (PE), continuous hemodiafiltration, and molecular adsorbent recirculating system (MARS), have been used in the treatment of liver failure.[7-9] In China, PE has been used as the main technique in patients suffering from liver failure for approximately 20 years.[10] In liver failure, a wide range of potentially toxic substances, including bilirubin, bile acid, short chain fatty acids, aromatic amino acids, cytokines, and ammonia, accumulate in the systemic circulation and are involved in multi-organ complications. Most of these toxins are bound to protein, especially to albumin (ALB).[11, 12] The most direct method to remove toxic substances is PE, where the toxic plasma is replaced with fresh normal plasma. PE also removes stimulatory factors released because of liver injury that are responsible for the increase of complications. Many studies have shown that PE reduces mortality,[1, 13] and recently the open, prospective, randomized, controlled study carried out by Larsen et al found that exchange of plasma in acute liver failure (ALF) patients with fresh frozen plasma increases transplant-free survival after 3 months.[14] However, no multicenter study in China with a large sample size has been carried out. The present prospective multicenter study was to evaluate the effect of PE on patients with HBV-ACLF.

Methods

Ethics statement

The research protocol was approved by the Human Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine, and all enrolled participants signed a written informed consent to participate in the study. Data were entered in duplicate a computerized database and analyzed anonymously.

Patients

Data of all the patients were recorded using case report forms, and medical monitors with source documentation were used for verifying the accuracy of the data collected. Consecutive patients diagnosed with HBV-ACLF were included. Eligible patients were from 10 hospitals from December 1, 2009 to December 31, 2011. The follow-up period for enrolled patients was one month after diagnosis of ACLF. All patients received antiviral treatment and complication treatment in the intensive care unit (ICU). Other conventional treatments included energy supplements, electrolyte maintenance and acid base equilibrium.

Inclusion and exclusion criteria

HBV-ACLF was diagnosed according to the Guidelines for Diagnosis and Treatment of Liver Failure in China (2006).[15] The inclusion criteria are: (1) age ranging from 18 to 65 years; (2) acute deterioration of preexisting chronic hepatitis B; (3) extreme fatigue with severe digestive symptoms such as obvious anorexia, abdominal distension, or nausea and vomiting; (4) progressively worsening jaundice within a short period of time [serum total bilirubin (TB) level ≥171 μmol/L or a daily elevation of ≥17.1 μmol/L]; (5) an obvious hemorrhagic tendency with prothrombin activity (PTA) ≤40%.

The exclusion criteria are: co-existed hepatitis with other causes, alcohol abuse, uncontrolled diabetes and heart diseases, malignancy and previous liver transplantation.

Definition and staging of ACLF

According to the Guidelines for Diagnosis and Treatment of Liver Failure in China (2006),[15] ACLF can be classified into early, middle, and end stages based on the severity of clinical manifestations. Early stage is defined as a progressively deepening jaundice (TB level ≥171 μmol/L or a daily increase of ≥17.1 μmol/L), PTA >30% but ≤40%, and no HE or other complications. Middle-stage disease represents progression of the symptoms of the early stage, including one of the following symptoms: grades I/II HE, ascites, or a PTA of >20% but ≤30%. In the end-stage disease, the condition deteriorates further with a PTA of ≤20% and includes one of the following symptoms: hepatic-renal syndrome, severe upper gastrointestinal bleeding, serious infection, and grades III/IV HE.