Therapeutic plasma exchange versus double plasma molecular absorption system in hepatitis B virus-infected acute-on-chronic liver failure treated by entecavir: A prospective study

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Abstract

Background: Therapeutic plasma exchange (TPE) and double plasma molecular absorption system (DPMAS) were two extracorporeal liver support systems. Few studies compared their efficacy profile.

Objective: This study was to compare the efficacy of TPE and DPMAS on acute-on-chronic liver failure (ACLF) caused by hepatitis B virus (HBV-ACLF).

Methods: 60 HBV-ACLF patients were enrolled and prospectively studied. All patients received entecavir therapy, and were assigned to TPE group (n = 33) and DPMAS group (n = 27). Primary end-points were the effects of TPE and DPMAS on liver function and serum inflammatory markers.

Results: Serum procalcitonin, interleukin (IL)-6, and high sensitive C-reactive protein (hsCRP) were significantly elevated in patients with HBV-ACLF. TPE achieved significantly higher removal rates of total bilirubin (TBIL, \( P = .002 \)), direct bilirubin (DBIL, \( P = .006 \)), and hsCRP (\( P = .010 \)) than DPMAS, but DPMAS displayed lower loss rate of albumin (\( P = .000 \)). TPE and DPMAS resulted in similarly increased serum IL-6 levels and comparable 12-week survivals (\( P > .05 \)). Multivariate analysis showed that hospital stay (Relative Risk [RR]: 1.062, 95% Confidence Interval [CI]: 1.011-1.115, \( P = .016 \)), prothrombin time (RR: 1.346, 95% CI: 1.077-1.726, \( P = .010 \)), and international normalized ratio (RR: 0.013, 95% CI: 0.006-0.788, \( P = .041 \)) were independent predictors for 12-week survival. Both TPE and DPMAS treatments were well-tolerated.

Conclusion: Compared to DPMAS, TPE was more efficient in eliminating TBIL, DBIL, and hsCRP, but it was associated with higher loss rate of albumin. TPE and DPMAS were similar in improving 12-week survivals in HBV-ACLF.

KEYWORDS
acute-on-chronic liver failure, artificial liver support system, C-reactive protein, double plasma molecular absorption system, interleukin-6, procalcitonin, therapeutic plasma exchange

1 INTRODUCTION

Acute-on-chronic liver failure (ACLF) is defined as an acute and severe deterioration of liver function in a patient with chronic liver disease, and it remains a therapeutic challenge with a 28-day mortality rates ranging from 29.7 to 40%.1-3 In China, over 80% of ACLF cases were caused by acute exacerbation of chronic hepatitis B due to a high prevalence of hepatitis B virus (HBV) infection.4,5 Up to date, liver transplantation (LT) remains the only definitive therapeutic option to salvage patients with ACLF. However, it is hampered by donor organ

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scarcity, complications of post-transplant immune rejection, and high cost.6

Artificial liver support system (ALSS) was first adopted to treat acute liver failure (ALF) in 1970s with the concept to replace the detoxification functions of the liver.7 It can provide temporary removal of an array of toxic substances and create an internal environment conducive to liver regeneration, bridging the failing liver to recovery or LT.8 During the last decades, many types of ALSSs, including therapeutic plasma exchange (TPE), hemoperfusion, continuous hemodiafiltration, molecular absorbents recirculating system (MARS) and fractionated plasma separation, absorption and dialysis system (FPSA), have been developed and applied to the treatment of liver failure.9 TPE is an extracorporeal procedure that involves separation of toxic plasma from the blood and replacement of equivalent amounts of fresh frozen plasma (FFP) and fluid. It is an attractive approach that has been widely employed to manage patients with liver failure for about two decades in China.10 Even though TPE has been reported to be effective in improving liver function and reducing mortalities of ALF11,12 and HBV-ACLF,10,13 it is restricted by requirement of large amount of good plasma, and risks of allergic reaction to plasma and blood-borne disease transmission.

Double plasma molecular absorption system (DPMAS) is an extracorporeal procedure that combines two hemoperfusion machines. During the procedure, toxic plasma is separated and cleansed by perfusion over two absorbers, and the final cleansed plasma is then returned to patients. It does not require large volumes of plasma and nor does it bear the risk of plasma-associated allergic reaction or disease transmissions. In comparison to TPE, DPMAS is more expensive (about 1,600 vs. 580 U.S. dollars per session) and time-consuming. And there remains great need to develop more efficient and specific absorbers of toxins accumulated in patients with liver failure. In the literature, few studies have directly compared the relative efficacy of both approaches with respect to toxin elimination.

This study aimed to investigate the efficacy and safety of DPMAS as compared to TPE for the treatment of patients with HBV-ACLF treated by entecavir (ETV).

2 | MATERIALS AND METHODS

2.1 | Patients

The study protocol was approved by the ethics committee of Second Affiliated Hospital of Kunming Medical University. Written informed consents were obtained from all enrolled patients and data were extracted from our electronic medical record system and analyzed anonymously.

A total of 112 consecutive patients received TPE and/or DPMAS in our unit between January 2014 and March 2016.

The primary diseases included ALF caused by ingestion of wild mushroom (n = 7), anti-tuberculosis drugs (n = 4), anti-hyperthyroidism (n = 3) drugs or traditional Chinese medicine (n = 14) and ACLF (n = 84). ALF was defined as rapid development of hepatic dysfunction, specifically coagulopathy with international normalized ratio (INR) ≥1.5 and mental alteration (encephalopathy) in a patient without preexisting cirrhosis and with an illness within 26 weeks.14 ACLF was defined as serum bilirubin ≥5 mg/dL and an INR ≥1.5 or prothrombin time activity (PTA)<40%, complicated within 4 weeks by ascites and/or hepatic encephalopathy (HE) in patients with previously diagnosed or undiagnosed chronic liver diseases.1 Cirrhosis was diagnosed according to medical history, physical examination, laboratory tests, and in combination with ultrasonography or computed tomography (CT).15 Exclusion criteria were: (1) co-infection with hepatitis A, C, D, E virus(HAV, HCV, HDV, HEV), or human immunodeficiency virus (HIV); (2) alcohol ingestion within 6 months; (3) uncontrolled diabetes or hypertension; (4) chronic heart, lung or kidney diseases; (5) malignancy including liver cancer; (6) age below 18 or above 65 years old; (7) past history of organ transplantation; (8) switching from TPE to DPMAS due to plasma shortage or allergy. Thus, 60 patients with HBV-ACLF were enrolled and prospectively studied in this study.

2.2 | Study design

Enrolled patients were divided into TPE group (n = 33), and DPMAS group (n = 27), respectively. All patients received standard medical therapy (SMT) in combination with TPE or DPMAS. During the study, blood samples were collected at admission, the day before and at the end of each session of TPE or DPMAS, and every 3-5 days in the hospital or at each clinic visit. When discharged, survived patients were followed up every 3-6 months in our unit or clinic, and additional visits were provided when a patient felt necessary. Each follow-up visit consisted of clinical assessment, routine blood tests and imaging tests. Deaths of patients were confirmed by contacts with their family members via telephone calls, emails, wechat, and QQchat as well as careful check in death registry.

2.3 | Treatments

2.3.1 | SMT

SMT aimed to treat the precipitating events and clinical problems complicated with liver failure. It included absolute bed rest, administration of hepatocyte protective and regenerative agents (i.e., glycyrrhizin, reduced glutathione, polyene phosphatidylcholine, and ademetionine), transfusion of human serum albumin and other blood constituents (i.e., red
blood cells (RBC), platelets (PLT), and FFP), maintenance of electrolyte or acid-base balances, treatment of bacterial infection with appropriate antibiotics. ETV was initiated in treatment-naïve patients with detectable HBV-DNA (>500 copies/ml).

2.3.2 | TPE

TPE was performed according to the requirements and procedures described in our previous studies. In brief, a double-lumen catheter was inserted into the femoral or internal jugular vein of patients. TPE was performed with plasma separator multifiltrate 3MUG7581 (Fresenius Medical Care AG & Co.KGAA, Furth Germany). About 3000 ml of plasma was exchanged and the plasma exchange rate was 20-30 ml/minute at each session. It was performed 2-3 times/week, lasting 2-3 h every session. Overall, 104 sessions of TPE were performed on 33 patients.

2.3.3 | DPMAS

DPMAS consists of a blood circuit and a plasma circuit. As illustrated in Figure 1, after insertion of a double-lumen catheter in the femoral or internal vein, plasma was separated from blood (blood circuit) by plasma separator multifiltrate 3MUG7581 (Fresenius Medical Care AG & Co.KGAA, Furth Germany) driven by a “blood pump” at a flow rate of 100-150 ml/minute. Subsequently, the patient’s plasma filtrate in the plasma circuit was perfused over a bilirubin adsorber (BS 330, Zhuhai health sails biotechnology co., LTD) and a macroporous neutral resin (HA330-II, Zhuhai health sails biotechnology co., LTD). The plasma circuit was driven by a “plasma pump” at a flow rate of 25-50 ml/min and purified plasma was finally returned to the patient’s body. It was also performed 2-3 times/week, lasting 2-3 h every session. Overall, 69 sessions of DPMAS were performed on 27 patients.

2.4 | Data collection

Patients’ demographic, laboratory and imaging data were extracted from our electronic medical record system and analyzed anonymously. Hemocytes including white blood cells (WBC), RBC, or hemoglobin (HGB) and PLT were counted at baseline and regularly. Serum parameters, including albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), direct bilirubin (DBIL), total bile acid (TBA), procalcitonin (PCT), interleukin-6 (IL-6), high sensitive C-reactive protein (hsCRP) were closely monitored at baseline, before and after each session of TPE or DPMAS; creatinine, prothrombin time (PT), INR, and electrolytes were tested at admission, every 3-5 days or at each follow-up visit; viral infection panel including HAV, HBV, HCV, HDV, HEV, and HIV was assayed at admission. For patients with chronic HBV infection, HBV-DNA, serologic tests for HBV were closely monitored every 3-6 months. All laboratory tests were carried out in the central laboratory department according to standard procedures and control. Imaging tests, including ultrasound or CT, were also performed every 3-6 months. Child–Turcotte–Pugh (CTP) and model for end-stage liver disease (MELD) scores were calculated according to published formulas. Removal rates (RRs) of biochemical parameters by a single treatment of TPE or DPMAS was calculated as: RRs = (pretreatment level-post-treatment level)/pretreatment level × 100%.

2.5 | Primary end points

Primary end-points were the effects of TPE and DPMAS on key liver function parameters (i.e., albumin, ALT, AST, TBA, TBIL, and DBIL) and serum inflammatory markers (i.e., PCT, IL-6, and hsCRP).

2.6 | Statistical analysis

Continuous values were described as mean ± standard deviation (SD) or medians, first and third quartiles, as appropriate.
All statistical analyses were performed by SPSS 17.0 software package (SPSS Inc, Chicago, IL). Continuous data were compared by Student’s t test or Mann-Whitney U test, and categorical variables were by χ² test. Survival analysis was executed by Kaplan-Meier method and log-rank test. Significant baseline predictors for survival were identified by univariate and multivariate analyses using the Cox proportional hazards regression model. A P value < .05 was considered significant.

3 | RESULTS

3.1 | Patient demographics

As shown in Table 1, baseline characteristics such as age, gender, serum albumin, PT, INR, TBIL, TBA, CTP scores, and MELD scores were similar between the two groups (P > .05).

3.2 | Impacts of a single treatment with TPE or DPMAS on liver function parameters

Overall, 104 sessions of TPE were performed on 33 patients and 69 sessions of DPMAS on 27 patients. All key liver function parameters, including albumin, ALT, AST, TBA, and DBIL, were reduced after a single treatment session in TPE group and DPMAS group (Table 2). The RRs of albumin (29.3 ± 9.7% vs. 15.8 ± 6.0%, P = .000), TBIL (41.3 ± 8.3% vs. 37.0 ± 9.1%, P = .002) and DBIL (41.9 ± 10.9% vs. 37.3 ± 10.6%, P = .006) were markedly higher in TPE group than DPMAS group, whereas those of
**3.3 Impacts of a single treatment with TPE or DPMAS on inflammatory markers**

After TPE treatment, serum PCT, IL-6 and hsCRP changed from 0.720 ± 0.809 ng/ml, 23.32 ± 19.03 pg/ml, and 22.01 ± 20.01 mg/l to 0.546 ± 0.548 ng/ml, 33.57 ± 30.00 pg/ml, and 12.25 ± 8.88 mg/l, respectively. Similar patterns were observed in DPMAS treatment (Table 2). In other words, TPE and DPMAS treatments resulted in marked reduction in serum PCT and hsCRP and significant increment in serum IL-6 (P < .05, Figure 2A-C). And the RRs of hsCRP were significantly higher in TPE group than DPMAS group (P = .010), whereas those of PCT and IL-6 were similar between the two groups (P > .05, Table 3).

**3.4 Impacts of TPE and DPMAS on patients’ survival**

During the study, a total of 42 patients died, with 24 in TPE group and 18 in DPMAS group. The median survival times were 12 weeks (95% confidence interval (CI):10.7-13.3) in TPE group and 11 weeks in DPMAS Group (95%CI: 9.3-12.7). The 4-week and 12-week survival rates in TPE group were 87.9% and 34.6%, respectively. There was no marked difference in survival between the two groups (P > .05, Table 3).

**3.5 Baseline predictors for survival at 12 weeks**

To identify the independent predictors for 12-week survival, we performed both univariate and multivariate analyses (Table 4). Baseline laboratory test results were taken as the date when the first session of TPE or DPMAS was performed. Univariate analysis revealed that hospital stay (relative risk (RR): 1.066, 95%CI: 1.026-1.108, P = .001),
baseline PT (RR: 1.308, 95% CI: 1.140-1.500, \( P = .000 \)), ALT (RR: 0.998, 95% CI: 0.997-1.000, \( P = .009 \)), AST (RR: 0.998, 95% CI: 0.997-1.000, \( P = .035 \)), TBIL (RR: 1.004, 95% CI: 1.001-1.007, \( P = .009 \)), DBIL (RR: 1.005, 95% CI: 1.001-1.009, \( P = .007 \)), and CTP score (RR: 1.246, 95% CI: 1.003-1.548, \( P = .047 \)) were significant predictors for 12-week survival. However, multivariate analysis showed that only hospital stay (RR: 1.062, 95% CI: 1.011-1.115, \( P = .016 \)), PT (RR: 1.346, 95% CI: 1.077-1.726, \( P = .010 \)), and INR (RR: 0.013, 95% CI: 0.006-0.788, \( P = .041 \)) remained significant predictors for 12-week survival.

### 3.6 Adverse events

Of the 173 sessions of TPE and DPMAS treatment, 2 sessions of TPE and 1 session of DPMAS were prematurely...
terminated due to irreversible blood clotting inside the extracorporeal circuit after 2 and 2.5 h of the treatment, respectively, which may be associated with inadequate heparin dosage, inappropriate extracorporeal blood circuit preparation, and low blood volume. During the treatment, 6 patients in TPE group and 2 in DPMAS group complained of nausea that resolved without special treatment. 3 patients in TPE group and 0 in DPMAS group showed signs of shock (lowered blood pressure, chills, sweating and palpitation) at the end of treatment, which was relieved by fluid infusion. After the treatment, 4 patients in TPE group and 1 in DPMAS group had overt hemorrhage at the puncture site, which was stopped by compression with or without infusion of FFP. Allergic reaction (skin rashes over the body, fever <38°C) occurred in 3 patients in TPE group, which was alleviated by administration of antihistamine. Overall, treatments of TPE and DPMAS were well-tolerated.

4 | DISCUSSION

In the present study, we observed that TPE and DPMAS treatments resulted in decreased liver function parameters (i.e., albumin, liver enzymes, TBA, TBIL, and DBIL) and inflammatory markers (i.e., PCT and CRP). In contrast, TPE and DPMAS treatments led to increased serum IL-6. Our results further demonstrated that TPE was more efficient in eliminating protein-bound toxins (i.e., TBIL, DBIL, TBA), and decreasing serum hsCRP. However, no difference in 12-week survival was detected between TPE and DPMAS treatments.

ACLF is a rapid and severe deterioration of liver function in patients with chronic liver disease. Patients with ACLF manifest as fatigue, loss of appetite, abdominal distention, jaundice, coagulopathy, HE, and ascites. Despite recent progress of medicine, ACLF remains a therapeutic challenge with extremely poor prognosis.\(^1\)\(^-\)\(^3\) The past decades witnessed the rapid development of ALSSs, which have emerged as an effective approach to managing patients with ACLF.\(^5\)\(^,\)\(^18\)

Previous studies reported that TPE resulted in a significant decrease in ALT, AST, TBIL, DBIL and TBA levels in treatment of ACLF patients.\(^10\)\(^,\)\(^19\) In our study, both TPE and DPMAS treatments were able to lower ALT, AST, TBIL, DBIL and TBA levels, which was consistent with these studies. However, with regard to albumin level, previous studies were inconsistent. After TPE treatment, Du et al. reported a significant increase in albumin level,\(^19\) Volkan et al. reported an insignificant change of albumin level,\(^20\) whereas Chen et al. reported that albumin was unchanged in early-stage ACLF patients and markedly increased in middle- and late-stage ACLF patients.\(^10\) In our study, we observed consistently that albumin was pronouncedly reduced after both TPE and DPMAS, with a higher reduction rate in TPE group than DPMAS group. Both TPE and DPMAS involve the separation of toxic plasma from whole blood. The plasma separator with a pore size of 0.2-0.6 μm allows passage of all plasma constituents, including albumin, fibrinogen, and immunoglobulins, which will be either discarded in TPE or perfused over absorptive materials (BS330 and HA330-II) to purify the toxin-loaded plasma that then will be recycled into the patients in DPMAS.\(^21\) Therefore TPE resulted in higher loss rate of albumin than DPMAS. Moreover, the detoxifying efficiency of the various ALSS is determined by a combination of several factors, including blood flow rates, surface, pore size and placement of filters, material, amount and active surface of absorbers, as well as albumin concentration and flow rates in the plasma circuits,\(^22\) which may explain the discrepancy among various studies.

Previous studies reported that ACLF was accompanied by an inflammatory profile, mimicking severe inflammatory response syndrome, featured by predominantly pro-inflammatory cytokines that are thought to mediate hepatic inflammation, apoptosis and necrosis of liver cells, cholestasis, and fibrosis, may lead to progression of stable cirrhosis to ACLF.\(^23\)\(^-\)\(^25\) PCT, IL-6 and CRP were non-specific inflammatory markers, particularly in patients with cirrhosis and bacterial infection.\(^26\) In our study, serum PCT, IL-6 and hsCRP levels were increased at baseline, consistent with previous studies,\(^26\)\(^,\)\(^27\) and PCT and hsCRP were decreased after both TPE and DPMAS, which was in agreement with previous studies.\(^28\) The explanation of higher removal rate of hsCRP by TPE than DPMAS may be due to higher loss rate of hsCRP in TPE, similar to that of albumin.

Up to date, the exact role of IL-6 in ACLF remains poorly understood. IL-6 is usually considered a pro-inflammatory cytokine, but it is also a pleiotropic cytokine that induces many biological activities. For example, it regulates the hepatic synthesis of a variety of acute-phase proteins and is also involved in the immunoregulatory disturbances in patients with chronic liver diseases.\(^29\)\(^,\)\(^30\) Previous studies suggested that IL-6 may promote hepatic regeneration after liver injury including liver cirrhosis and partial hepatectomy.\(^31\)\(^,\)\(^32\) Data on the effect of ALSS on serum IL-6 levels are controversial. Previous studies reported that TPE reduced the elevated serum levels of IL-6 in patients with ALF,\(^33\)\(^,\)\(^34\) Martirosyan et al. showed that TPE increased IL-6 mRNA transcripts in monocytes from patients with antiphospholipid syndrome, restoring the mRNA expression levels to within normal ranges,\(^35\) whereas Vanessa et al. showed that FPSA and MARS failed to change serum IL-6 levels significantly in patients with ACLF despite IL-6 was removed by the two systems, and the discrepancy was probably due to a high rate of cytokine production in ACLF patients.\(^36\) However, few studies investigated the effect of TPE and DPMAS on serum levels of IL-6 in ACLF patients. Our results showed that serum IL-6 was consistently increased after both
TPE and DPMAS, which may be due to increased production and impaired elimination rates of IL-6 in HBV-ACLF patients, higher than removal rates by TPE and DPMAS.

A recent meta-analysis reported that ALSSs could improve 1-month and 3-month survivals in patients with ACLF. Previous studies also reported that TPE significantly reduced the 1-month and 3-month mortality rates of ACLF patients. Our study demonstrated that DPMAS had similar effects on 1- and 3-month survival rates to that of TPE in treatment of HBV-ACLF patients.

Chen et al. reported that age, disease stage, TBIL, Cr and PT levels were independent predictors for 1-month mortality among HBV-ACLF patients. Wan et al. reported that HE, ascites, TPE therapy, and MELD scores were independent risk factors for 3-month mortality for HBV-ACLF patients. In our study, we found that hospital stay, PT and INR were independent predictors for mortality at 12 weeks. The most frequent adverse events reported in ALSS treatments include bleeding, hypotension, infection, coagulopathy, and respiratory failure. In our study, respiratory failure was not observed, and frequencies of adverse events such as overt bleeding, hypotension, fever were not different between TPE and DPMAS groups.

Our study had the following limitations. First, the sample numbers in TPE and DPMAS groups were limited. Second, the group assignment was non-randomized. Third, we only measured one pro-inflammatory cytokine IL-6, which could not reflect the complete cytokine profile in HBV-ACLF.

In conclusion, our study showed that DPMAS and TPE were both effective and safe therapeutic approaches for HBV-ACLF patients treated by ETV. Despite TPE resulted in higher removal rates of TBIL, DBIL, and hsCRP, but it was disadvantageous in terms of requirement of large volumes of FFP, risk of plasma allergies and blood-borne disease transmission, and higher loss rate of albumin than DPMAS.

ETHICAL STANDARDS

All study procedures were in accordance with the ethical standards of the ethics committee of the Second Affiliated Hospital of Kunming Medical University on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES


