Comparison of plasma exchange, double plasma molecular adsorption system, and their combination in treating acute-on-chronic liver failure

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Abstract

Objective: Our objective was to compare the effectiveness of nonbiological artificial liver (NBAL) support, particularly short-term (28-day) survival rates, in patients who underwent treatment using double plasma molecular adsorption system (DPMAS), plasma exchange (PE), or combined PE+DPMAS, in addition to comprehensive physical treatment for different stages of acute-on-chronic liver failure (ACLF).

Methods: We retrospectively reviewed clinical data of 135 patients with ACLF who received NBAL treatment between November 2015 and February 2019. The patients were categorized into PE, DPMAS, and PE+DPMAS groups. Short-term effectiveness of treatment was assessed and compared based on selected clinical findings, laboratory parameters, and liver function markers.

Results: Coagulation function improved significantly in all groups after treatment. In the PE and PE+DPMAS groups, prothrombin time decreased to different degrees, whereas plasma thromboplastin antecedent increased significantly after treatment. White blood cell counts increased and platelet counts decreased in all groups after treatment. The model for end-stage liver disease score, Child–Pugh grade, systematic inflammatory syndrome score, and sepsis-related organ failure score decreased in all three groups after treatment.

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Conclusions: PE, DPMAS, and PE+DPMAS improved disease indicators in all patients with ACLF. The combined treatment improved the short-term effectiveness of treatment, especially in patients with mild ACLF.

Introduction

Liver failure is defined as the presence of coagulation disorders, jaundice, hepatic encephalopathy, and ascites that result from the serious liver injury. Serious dysfunction and decompensation of the functions of synthesis, detoxification, excretion, and biotransformation result in hepatic injuries.[1,2] Acute-on-chronic liver failure (ACLF) is the most common type of liver failure in China,[3] with an incidence of 2.53 per 100,000 individuals; ACLF is associated with rapid progression and high mortality.[4,5]

Nonbiological artificial liver (NBAL) refers to a treatment method using an *ex vivo* mechanical, physicochemical, or biological device that removes toxic substances, supplies essential substances, and improves the internal environment, thus replacing the functions of the failing liver temporarily.[6–8] NBAL may alleviate the burden on the liver and help restore liver function or it may buy time to provide opportunities for liver transplantation.

To date, NBAL has widely been applied in clinical practice, with its effectiveness being demonstrated in several studies.[6–9] Plasma exchange (PE) is the most common NBAL technique used in China. It uses a plasma separator to filter the plasma from full blood to remove toxic substances dissolved in the plasma or adsorbed by plasma proteins. Fresh frozen plasma is then supplied to replace coagulation factors and albumin (ALB).[10–12] The double plasma molecular adsorption system (DPMAS) uses a plasma filter to continuously separate the plasma; the filtered plasma passes through the specific bilirubin adsorber BS330 and the macroporous resin hemoperfusion device HA330-II to specifically remove toxic metabolites, including large and medium-size soluble bilirubins and inflammatory mediators. The plasma is then transfused back to the body without substitution fluid or plasma, which could help regeneration of hepatocytes.[13,14]

DPMAS is a relatively new technology and exact outcomes still need to be defined. To extract maximum clinical benefit from NBAL, various approaches are being tested. One such modality is a combination therapy using PE and DPMAS. A recent retrospective analysis identified that PE+DPMAS was effective in improving short-term survival rates in patients with moderate-to-severe disease.[13] Another critical report, although retrospective in nature, suggested that PE+DPMAS is safe with a lesser quantity of plasma.[14] A case report concluded that PE+DPMAS could be an effective treatment to prevent an emerging thyroid storm with severe liver injury.[15] Several other reports have documented the failure of drug treatments in improving short-term survival rates in hepatitis B patients with ACLF; PE reportedly

decreased the short-term mortality in these patients.[16]

Based on this limited evidence, we designed the present study to retrospectively analyze and compare the effectiveness of NBAL techniques such as PE, DPMA, or PE+DPMA in addition to comprehensive physical treatment of different stages of ACLF, particularly short-term (28-day) survival rates.

Material and methods

Study design and patients

Clinical data of patients with ACLF hospitalized at the Gastroenterology Department of Second Affiliated Hospital of Kunming Medical University (Kunming, China) between November 2015 and February 2019 were retrospectively reviewed. The patients were categorized into PE, DPMAS, and PE+DPMAS groups, according to the type of NBAL technique they underwent. The study protocol was reviewed and approved by the ethics committee of our hospital.

The clinical diagnosis of all patients was in agreement with the diagnostic criteria of ACLF described in the Chinese Medical Association *Guidelines for Diagnosis and Treatment of Liver Failure*.[2,4] The patients showed symptoms of liver failure, as manifested by an acute worsening of jaundice and coagulation disorders in addition to the underlying liver disease, which could be accompanied by complications such as hepatic encephalopathy, ascites, electrolyte disturbance, infection, hepatorenal syndrome, hepatopulmonary syndrome, as well as extrahepatic organ failure. Jaundice in patients worsened rapidly, with total serum bilirubin (TBIL) ≥ 10 times the upper limit of normal or increasing by $\geq 17.1\,\mu mol/L$ per day, and the patients had hemorrhagic manifestations, with plasma thromboplastin antecedent (PTA) $\leq 40\%$ or an international normalized ratio (INR) ≥ 1.5. Data of patients with the following conditions were excluded: (1) severe cardiac, cerebral, or pulmonary diseases, or with active bleeding, or accompanied with disseminated intravascular coagulation; (2) acute, subacute, or chronic liver failure; (3) allergy to blood products or drugs (such as plasma, heparin, and protamine) used during artificial liver; or (4) pregnancy.

Treatment methods

All patients underwent thorough clinical examinations upon admission. They received comprehensive physical treatments, including bed rest, liver protection, enzyme reduction, and removal of bilirubin. In addition, sufficient vitamins were provided, and water, electrolyte, and acid-base balances were maintained. Infection was actively controlled. Appropriate measures were taken to prevent complications such as encephaledema, hepatic encephalopathy, renal dysfunction, and bleeding. Entecavir (0.5 mg/d; Sino-US Shanghai Squibb Pharmaceutical Co. Ltd., Shanghai, China) was provided for all patients with hepatitis B virus (HBV)-DNA $\geq 1.0 \times 10^4$ copies/mL. Drug therapy was indicated per the HBV-DNA levels as recommended by the 2015 *Guidelines for the Prevention and Treatment of Chronic Hepatitis B* issued jointly by the Chinese Society of Hepatology, Chinese Medical Association, and Chinese Society of Infectious Diseases.[17] Treatments with different types of artificial liver were conducted in addition to the comprehensive physical treatments.

In the PE group, an artificial liver supporting system (Jianfan Biotechnology Co. Ltd., Zhuhai, China), a membrane plasma separator (Belk Co. Ltd., Italy), and a blood circuit catheter (Hanaco Medical Co. Ltd., Tianjin, China) were used. A single-needle, two-chamber catheter was

used for femoral vein catheterization to establish *ex vivo* blood circulation. Oxygen inhalation and electrocardiograph monitoring were conducted throughout the operation. Venous blood was obtained before and after treatment for routine blood work, liver and renal function tests, coagulation, blood ammonia, C-reactive protein (CRP), and procalcitonin. The peripheral circulation canal was pre-rinsed. Patients received an intravenous (IV) injection of heparin (loading dose of 20 mg) and dexamethasone (5 mg), and an IV drip of 10% calcium gluconate was introduced to prevent hypocalcemia. The dose of heparin was adjusted according to the disease course, transmembrane pressure, plasma separation velocity, and prothrombin time (PT), and was pumped at 4 to 8 mg/hour. The velocity of blood flow was 100 to 120 mL/minute, and plasma separation velocity was 20 to 30 mL/minute. For each time of plasma replacement, 2500 to 3500 mL of fresh frozen plasma and 10 g of human ALB were administered. The treatment time was about 3 hours.

The same instruments were used for the DPMAS group as in the PE group. The plasma separator was linked to the BS330 bilirubin adsorber and HA330-II macroporous resin hemoperfusion device (Jianfan Biotechnology Co. Ltd.). The treatment time was about 3 hours.

For PE+DPMAS, PE was conducted using half-volume plasma replacement (1000–1500 mL). After PE was completed, DPMAS treatment was conducted sequentially. One treatment session took 4 to 4.5 hours. The interval between treatments for an individual patient in all groups ranged from 1 to 4 days.

Data collection

Changes in signs and clinical symptoms, including jaundice, feebleness, poor appetite, abdominal distension, and hepatic encephalopathy were observed and compared before and after treatment. Routine blood results, coagulation functions, liver and renal function markers, inflammatory indices [including white blood cells (WBC), hemoglobin, platelets (PLT), PT, PTA, INR, TBIL, alanine transaminase, aspartate transaminase, γ-glutamyl transferase, alkaline phosphatase, ammonia, creatinine, blood urea nitrogen, procalcitonin, and CRP], model for end-stage liver disease (MELD) score, 28-day survival rate, TBIL reduction rate, systemic inflammatory response syndrome (SIRS) score, sepsis-related organ failure (SOFA) score, Child–Pugh liver function stage, and stage of chronic hepatitis before and after treatments were recorded and compared. Adverse reactions that emerged during treatment were monitored and clinical outcomes assessed.

Treatment effectiveness assessment criteria

Short-term effectiveness of treatment was assessed based on selected clinical parameters immediately at the end of artificial liver treatment.[4] The recommendations provided in the 2018 Chinese Medical Association *Guidelines for the Diagnosis and Treatment of Liver Failure* were followed. Treatment was considered effective if there was substantial improvement in the following parameters: (1) clinical symptoms, including feebleness, poor appetite, and abdominal distension, and absence of hepatic encephalopathy; (2) signs including jaundice and ascites; and (3) liver function indices and reduction in serum TBIL by >40.0% (PTA >40% or INR <1.5). Treatment was considered ineffective if the following criteria were met: (1) clinical symptoms and signs including feebleness, poor appetite, and abdominal distension worsened; (2) liver function indices increased; (3) new complications or

extrahepatic organ failure arose; or (4) the pre-existing complications worsened.

Statistical analysis

SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Categorical data were described in numbers and percentages and analyzed using the chi-square or Fisher exact test, as appropriate. Tests for normality and homogeneity of variance were conducted for continuous data. For normally distributed data, the paired *t*-test was used for before/after intra-group comparisons, whereas intergroup comparisons were made using analysis of variance (ANOVA) and the least significant difference (LSD) post hoc test. The rank sum test was used for the comparisons of non-normally distributed continuous data. The Spearman rank correlation test was used for correlation analysis. $P < 0.05$ was considered statistically significant.

Results

Characteristics of the patients

A total of 135 patients with ACLF met the inclusion criteria; of these, 45 patients received PE (32 men and 13 women), 42 were in the DPMAS group (30 men and 12 women), and 48 cases in the PE+DPMAS group (33 men and 15 women). The mean age of patients was 42.6 ± 14.5 (range: 22–81) years, 43.8 ± 11.5 (range: 25–69) years, and 41.6 ± 12.4 (range: 17–80) years, respectively, among the groups. Underlying liver diseases of HBV infection, alcoholic liver disease, autoimmune liver disease, drug-induced liver disease, and other liver diseases were reported in 57, 49, 11, 8, and 10 patients, respectively. Eighty-two patients reported complications, including co-infection, hepatic encephalopathy, and hepatorenal syndrome in 51, 20, and 11 patients, respectively. The general data of the three groups of patients were compared and the differences were not significant.

Artificial liver treatment

For the 45 patients in the PE group, 103 PE treatments were administered, with a mean of 2.3 treatments/patient. For the 42 patients in the DPMAS group, a total of 105 DPMAS treatments were administered, for a mean of 2.5 treatments/patient. For the 48 patients in the PE+DPMAS group, 96 PE treatments were administered, for a mean of 2.0 treatments/patient.

Treatment effectiveness

Table 1 shows the effective rates and the 28-day survival rates of patients in the PE, DPMAS, and PE+DPMAS groups

Table 1. Comparison of treatment effectiveness of different artificial liver strategies according to stage of liver failure.

Liver failure stage	PE (n = 45)	DPMAS (n = 42)	PE+DPMAS (n = 48)	P
Effective rate (%)				
Mild	12/21 (57.1)	12/24 (50.0)	22/26 (84.6)	0.026
Moderate	9/19 (47.4)	5/13 (38.5)	11/21 (52.3)	0.732
Severe	3/11 (27.2)	1/6 (16.7)	2/9 (22.2)	0.252
28-day survival rate (%)				
Mild	12/21 (57.1)	12/24 (50.0)	22/26 (84.6)	0.026
Moderate	9/19 (47.4)	5/13 (38.5)	11/21 (52.3)	0.732
Severe	2/11 (18.2)	1/6 (16.7)	2/9 (22.2)	0.958

according to different stages of liver failure. The effective rates and 28-day survival rates were significantly different among the three strategies in patients with mild ACLF (PE: 57.1% vs. DPMAS: 50.0% vs. PE+DPMAS: 84.6%, $P = 0.026$). There were no differences among the three strategies in patients with moderate or severe liver failure.

Coagulation, liver function tests, and routine blood work before and after treatments

Coagulation function improved significantly in all three groups. In the PE and PE+DPMAS groups, PT decreased to different degrees (PE: $P = 0.025$; PE+DPMAS: $P = 0.010$), whereas PTA increased significantly after treatments (PE: $P = 0.032$; PE+DPMAS: $P = 0.010$). Liver function of patients in all three groups improved significantly after treatments. WBC increased (DPMAS: $P = 0.039$; PE: $P = 0.043$; PE+DPMAS: $P = 0.045$) and PLT decreased (DPMAS: $P = 0.041$; PE: $P = 0.035$; PE+DPMAS: $P = 0.042$) in all groups after treatment. The MELD score (DPMAS: $P = 0.028$; PE: $P = 0.032$; PE+DPMAS: $P = 0.025$), Child–Pugh grade (DPMAS: $P = 0.038$; PE: $P = 0.034$; PE+DPMAS: $P = 0.029$), SIRS (DPMAS: $P = 0.041$; PE: $P = 0.041$; PE+DPMAS: $P = 0.039$), and SOFA (DPMAS: $P = 0.032$; PE: $P = 0.042$; PE+DPMAS: $P = 0.031$) decreased in all groups after treatment (Table 2).

Discussion

This study aimed to analyze the effectiveness of NBAL using DPMAS, PE, or PE+DPMAS in addition to comprehensive physical treatment of different stages of ACLF. The results suggest that PE, DPMAS, and PE+DPMAS improved disease indicators in all patients with ACLF. The 28-day survival rates observed among the study population indicated that PE+DPMAS may significantly reduce mortality in patients with mild ACLF.

Effective treatments are still lacking for liver failure, and liver transplantation is not the treatment of choice in most patients because of various complications, including donor liver shortage, high cost, and unsuitable medical condition.[18] Fortunately, with advances in NBAL techniques, the success rate of treatment in patients with ACLF has increased greatly.[19] PE is the most commonly used mode of artificial liver in China.[4] PE not only clears toxic substances resulting from liver failure but also supplies various bioactive substances. However, the efficacy of PE in removing water-soluble toxins, including blood ammonia, creatinine, and inflammatory mediators, is relatively poor.[20,21] Therefore, PE is less effective for treating complications such as hepatic encephalopathy and hepatorenal syndrome. In addition, the infusion of large amounts of stored plasma can lead to the accumulation of citrates, which in turn increases the risk of metabolic alkalosis and encephaledema.[21]

DPMAS is a new plasma adsorption system that combines broad-spectrum plasma adsorption with specific bilirubin adsorption; it can effectively remove bilirubin and toxic metabolites such as cytokines, endotoxins, aromatic amino acids, and blood ammonia.[13,14,22–24] In this study, we observed a >40% reduction in TBIL after DPMAS treatment, which is in agreement with previous studies.[13,14,22–24] In contrast, DPMAS cannot supply beneficial substances such as coagulation factors and ALB. Furthermore, high affinity between adsorption proteins and toxins can increase depletion of ALB in DPMAS. A prospective comparative trial showed that PE, although causing a large loss of ALB, was more efficient than DPMAS in eliminating bilirubins

Table 2. Comparison of coagulation function and biochemical indicators before and after artificial liver treatments.

	DPMAS group (n = 42)			PE group (n = 45)			PE+DPMAS group (n = 48)			
	Before treatment	After treatment	P	Before treatment	After treatment	P	Before treatment	After treatment	P	P intergroup
Prothrombin time (s)	22.36 ± 14.44	16.73 ± 15.59	0.133	22.63 ± 8.93	12.52 ± 8.38	0.025	23.07 ± 7.74	15.12 ± 10.67	0.010	0.026
Plasma thromboplastin antecedent (μg/mL)	43.56 ± 22.38	54.21 ± 20.37	0.141	44.30 ± 22.50	60.05 ± 18.25	0.032	44.80 ± 26.41	56.60 ± 14.98	0.010	0.029
International normalized ratio	2.55 ± 0.73	1.81 ± 0.39	0.182	2.96 ± 1.02	1.25 ± 0.43	0.027	2.98 ± 1.05	1.23 ± 0.41	0.013	0.031
Total bilirubin (μmol/L)	260.94 ± 115.38	155.61 ± 59.46	0.024	279.38 ± 127.95	143.78 ± 51.39	0.029	288.52 ± 169.48	132.26 ± 91.51	0.010	0.412
Ammonia (μmol/L)	63.82 ± 48.65	39.12 ± 42.44	0.026	59.37 ± 50.37	46.36 ± 35.20	0.031	62.35 ± 44.68	37.63 ± 38.34	0.021	0.536
Alanine transaminase (IU/L)	1003.90 ± 280.15	282.25 ± 233.01	0.012	1247.39 ± 367.65	312.90 ± 241.98	0.015	1163.66 ± 405.24	280.20 ± 215.48	0.011	0.782
Aspartate transaminase (IU/L)	514.30 ± 180.98	166.71 ± 107.18	0.025	667.99 ± 294.46	225.01 ± 289.95	0.023	611.76 ± 306.59	202.90 ± 266.53	0.021	0.831
Alkaline phosphatase (IU/L)	134.90 ± 37.83	111.96 ± 22.90	0.039	101.42 ± 62.01	72.50 ± 18.22	0.031	148.63 ± 65.29	110.90 ± 46.05	0.035	0.629
γ-Glutamyl transferase (U/L)	185.70 ± 204.28	110.17 ± 85.25	0.049	173.18 ± 218.68	89.50 ± 49.45	0.045	174.76 ± 161.16	98.90 ± 92.23	0.041	0.721
Total bilirubin decrease rate (%)		48.2 ± 10.3			49.6 ± 10.2			58.2 ± 11.0		
Creatinine (μmol/L)	216 ± 124	141 ± 100	0.027	198 ± 122	175 ± 100	0.034	223 ± 131	129 ± 98	0.021	0.356
Blood urea nitrogen (mmol/L)	22.75 ± 12.01	13.56 ± 9.72	0.026	21.85 ± 12.76	16.29 ± 10.23	0.048	23.91 ± 13.42	11.75 ± 9.52	0.024	0.389
White blood cells (×10⁹/L)	9.97 ± 4.58	12.85 ± 6.52	0.039	10.90 ± 3.33	11.86 ± 3.15	0.043	11.78 ± 4.44	12.07 ± 5.68	0.045	0.472
Platelets (×10⁹/L)	114.2 ± 54.5	99.0 ± 47.9	0.041	116.5 ± 67.1	98.3 ± 58.5	0.035	112.3 ± 66.8	99.4 ± 64.3	0.042	0.297
Hemoglobin (g/L)	125 ± 17	112 ± 17	0.029	122 ± 20	105 ± 18	0.025	125 ± 20	114 ± 16	0.031	0.331
MELD score	25.9 ± 5.6	18.9 ± 5.4	0.028	26.5 ± 6.0	19.1 ± 5.3	0.032	27.8 ± 6.3	16.3 ± 4.4	0.025	0.294
Child-Pugh grade	11.3 ± 2.6	7.5 ± 1.9	0.038	11.9 ± 2.7	7.4 ± 1.5	0.034	12.0 ± 2.7	6.7 ± 1.6	0.029	0.365
SIRS score	1.8 ± 0.5	0.6 ± 0.4	0.041	1.8 ± 0.5	0.6 ± 0.4	0.041	1.8 ± 0.5	0.6 ± 0.4	0.039	0.287
SOFA score	7.3 ± 3.2	2.9 ± 1.5	0.032	7.1 ± 3.0	3.1 ± 1.5	0.042	7.6 ± 3.3	2.5 ± 1.4	0.031	0.452

DPMAS, double plasma molecular adsorption system; PE, plasma exchange; MELD, model for end-stage liver disease; SIRS, systemic inflammatory response syndrome; SOFA, sepsis-related organ failure.

and CRP. That study indicated that 12-week survival rates were not significantly different between PE and DPMAS groups.[25]

Combining PE and DPMAS could compensate for the drawbacks of the two techniques. In our study, for patients with mild ACLF, the PE+DPMAS treatment was significantly more effective than using PE or DPMAS alone. Combined application of PE and DPMAS not only reduces the PE volume but also appears to improve the short-term effectiveness of treating liver failure. This finding was supported by a pilot study of PE+DPMAS.[22] Although that study did not use a multi-strategy comparison, as in the present study, the authors used regional citrate anticoagulation. In our study, the PE+DPMAS treatment was no more effective than PE or DPMAS alone for patients with moderate and severe liver failure. The advantages of PE and DPMAS could complement each other. A comparative study of clinical efficacy of PE and PE+DPMAS in a cohort of 67 Chinese patients with severe hepatic failure demonstrated that the combined techniques substantially improved 24-day survival rates along with the option of using less plasma.[26] Improvements in coagulation functions and considerable removal of bilirubin and bile acids were observed. Therefore, PE+DPMAS could maximize treatment success for patients with liver failure.

Six patients in the PE group, three in the PE+DPMAS group, and none in the DPMAS group had plasma allergy. An increase in WBC, to different degrees, was found in all three groups, which could be associated with the routine administration of 5 mg of dexamethasone before treatment. The PLT level decreased in all three groups compared with baseline. Although the underlying mechanisms are unclear, we speculate that this could be associated with anticoagulation agents.[27] Both PE and DPMAS can damage blood cells.[28] The findings of this study also showed that the combined application of PE and DPMAS had superimposed effects, which could be associated with blood cell damage caused by the separator and adsorption columns, as well as by the increased anticoagulation time induced by heparin.

Even though our findings are important, this study has several limitations. The sample size was relatively small and the follow-up period was short. The retrospective nature of the study limited analysis of data to that found in the medical charts. Clinical and laboratory parameters were available only for the pre- and post-treatment timeframes; no information was available for parameters during treatment.

In conclusion, the 28-day survival rate in our study population clearly indicated that treatment with PE+DPMAS could increase the short-term effective rate of artificial liver treatment for ACLF, especially in patients with mild ACLF. These results should be confirmed in larger, prospective trials.

Declaration of conflicting interest

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