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RESEARCH ARTICLE

Therapeutic effect of double plasma molecular adsorption system and sequential half-dose plasma exchange in patients with HBV-related acute-on-chronic liver failure

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Abstract

Objective: The artificial liver support system (ALSS) is used frequently as a first-line treatment for hepatitis B virus-associated acute-on-chronic liver failure (HBV-ACLF). This study aims to compare the therapeutic efficacy of double plasma molecular adsorption system (DPMAS) with sequential half-dose plasma exchange (PE) (DPMAS+PE) and full-dose PE in patients with HBV-ACLF.

Methods: A total of 131 hospitalized patients who were diagnosed with HBV-ACLF and underwent DPMAS+PE or PE were retrospectively analyzed. According to the treatment methods used, they were divided into PE group ($n = 77$) and DPMAS+PE group ($n = 54$). The main evaluation indexes included the change of liver function and the 28-days liver transplant-free survival rates after the different treatments.

Results: There were no significant differences on severity of illness between PE group and DPMAS+PE group ($P > 0.05$). The total bilirubin (TBIL) levels immediately after treatment, and at 24 and 72 hours after treatment were markedly decreased in DPMAS+PE group than that in PE group ($52.3 \pm 9.4\%$ vs $42.3 \pm 7.2\%$, $P < 0.05$; $24.2 \pm 10.0\%$ vs $13.5 \pm 13.0\%$, $P < 0.05$; $24.8 \pm 13.1\%$ vs $14.9 \pm 14.9\%$, $P < 0.05$; respectively). The 28-days survival rates was 62.3% and 72.2% in PE and DPMAS+PE groups ($P = 0.146$). Furthermore, the 28-days survival rates were significantly higher in DPMAS+PE group than that in PE group (57.4% vs 41.7%, $P = 0.043$) in the intermediate-advanced stage patients.

Conclusion: Compared with PE alone, DPMAS+PE might more effectively improve temporary TBIL in ACLF patients, and improve the 28-days survival rates in HBV-ACLF patients with intermediate-advanced stage. Therefore, DPMAS+PE may be an available ALSS treatment for HBV-ACLF patients.

KEYWORDS

acute-on-chronic liver failure, artificial liver support, double plasma molecular absorption system, plasma exchange

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1 | INTRODUCTION

Acute-on-chronic liver failure (ACLF) is defined as the appearance of jaundice and/or coagulopathy as the initial clinical manifestation of acute liver damage, on the basis of chronic hepatic disease known or not yet known, with ascites and/or hepatic encephalopathy within 4 weeks of onset.[1] It is a common severe liver disease syndrome and progresses rapidly, with a short-term mortality rate of 50% to 90%.[2] In China, hepatitis B virus (HBV) infection is a main inducer of ACLF[3], the mortality rate is high. Liver transplantation is currently the only effective treatment, but it is limited by the lack of donors.[4] Therefore, the artificial liver support system (ALSS) is used frequently as a first-line treatment for HBV-ACLF to promote liver function recovery or act as a bridge for liver transplantation.[5,6]

ALSS utilizes in vitro mechanical, chemical, or biological devices to temporarily and partially replace the liver function, create conditions for hepatocyte regeneration and spontaneous recovery of liver function, and extend the waiting time in patients with liver failure for liver transplantation, and thus is considered an effective means of transition therapy.[7] Among the ALSS methods, nonbiological artificial liver (NBAL) is the most mature technique and used most frequently in clinical practice.[8,9] Previous studies have confirmed NBAL combined with medical treatment can effectively improve the liver function and decrease the mortality in patients with liver failure.[10,11] Plasma exchange (PE) is a widely used NBAL technique, which separates and discards the patient's plasma from the whole blood by a membrane-type plasma separator and then supplements the same amount of fresh frozen plasma. It can nonspecifically remove the medium- and small-molecule metabolic toxins, and it can also supplement the essential substances such as albumin and coagulation factors that are lacking in the patients, thus it can replace some functions of the liver.[12] However, PE is often limited due to inadequate plasma supply. Therefore, clinicians are actively searching for plasma substitutes. Agreda et al.[13] used the hydroxyethy starch combined with albumin as a replacement solution in the initial replacement in PE.

Based on bilirubin adsorption therapy, the double plasma molecular adsorption system (DPMAS) adds a broad-spectrum adsorption column that can adsorb medium- and macro-molecular toxins, that is, combining two kinds of adsorbents, neutral macroporous adsorption resin (HA330-II, Zhuhai health sails biotechnology co., Ltd, Zhuhai, China) and ion exchange resin (BS330, Zhuhai health sails biotechnology co., Ltd, Zhuhai, China) for plasma adsorption therapy. The resin in HA330-II blood perfusion device is a broad-spectrum adsorbent, which can adsorb medium- and macro-molecular toxins such as inflammatory mediators while the resin in BS330 adsorption column is a specific adsorbent for bilirubin. A prospective study[14] showed that, compared with DPMAS, PE could reduce bilirubin more effectively, but was accompanied by a higher albumin loss. At present, there is no study comparing the efficacy profile between DPMAS with sequential half-dose PE (DPMAS+PE) and full-dose PE. This study aims to investigate the differences in improving the liver function between DPMAS+PE and PE in the treatment of ACLF.

2 | MATERIALS AND METHODS

2.1 | Research subjects

This is a retrospective study. We collected all hospitalized patients ($n = 144$) who were diagnosed with HBV-ACLF and underwent DPMAS+PE or PE from June 2016 to June 2018 at the YouAn Hospital of Capital Medical University, Beijing, China. The inclusion criteria were (a) patients with ACLF caused by HBV infection; and (b) patients satisfying the diagnostic criteria for ACLF by the Asian Pacific Association for the Study of the Liver [1] The exclusion criteria were (a) patients with previous liver transplantation; (b) patients complicated with underlying diseases such as severe heart, respiratory, and blood system diseases; and (c) patients complicated with malignant tumors. Seven patients were excluded due to alcoholic hepatitis and six patients were excluded due to upper gastrointestinal bleeding. As a result, a total of 131 patients were included for analysis.

According to the treatment methods used, the patients were divided into PE group and DPMAS+PE group. Seventy-seven patients in the PE group received 171 treatments, with 41 patients in the early stage, 33 patients in the intermediate stage, and 3 patients in the advanced phase. Fifty-four patients in the DPMAS+PE group received 124 treatments, with 29 patients in the early stage, 21 patients in the intermediate stage, and 4 patients in the advanced stage. And $30\% \leq$ prothrombin activity (PTA) $< 40\%$ was defined as early stage, $20\% \leq PTA < 30\%$ was defined as intermediate stage, and $PTA < 20\%$ was defined as advanced stage.[15]

This study followed the principles of the Helsinki Declaration and was approved by the Ethics Committee of Beijing YouAn Hospital affiliated to Capital Medical University. For all treatments, written informed consent was obtained from the patients or their family members.

2.2 | Treatment methods

2.2.1 | Comprehensive medical treatment

All the 131 patients enrolled received comprehensive medical treatment after admission to the hospital, including general supportive treatment, anti-viral treatment, energy and vitamin supplementation, supplementation of blood products, such as albumin and plasma, and treatment of potential complications.

2.2.2 | Artificial liver treatment

The Plasauto IQ-21 blood purification device and indispensable accessories (Asahi Kasei Medical Co., Ltd, Tokyo, Japan) were used for PE, and the plasma separator Plasmaflo-OP-08W

(Asahi Kasei Medical Co., Ltd, Tokyo, Japan) was applied. Blood pumping speed was 120 to 150 mL/min, the plasma separating speed was 25 to 30 mL/min, and the plasma separation ratio was 30%. Prior to PE, 25 mg promethazine hydrochloride was routinely administered via intramuscular injection to prevent plasma allergy. DPMAS was applied using the Plasauto IQ-21 device. Briefly, the blood first flowed through the Plasmaflo-OP-08W plasma separator after being pumped out of the body at a plasma separation speed of 25 to 30 mL/min, and the plasma then flowed sequentially through the ion exchange resin (BS330) and the neutral macroporous adsorption resin (HA330-II), and was mixed with the blood cells and infused back into the patient, with a blood pumping speed of ≈160 mL/min during the treatment. The plasma volume for a single treatment by DPMAS was approximately 5.5 to 6 L. The PE group was treated with PE alone, and the amount of fresh frozen plasma was 2200 to 2400 mL per treatment, and the time for a single treatment was about 2 hours. The DPMAS +PE group was treated with DPMAS first, followed by sequential PE treatment, with the fresh frozen plasma volume of 1100 to 1200 mL for each treatment, and the time for a single treatment was about 3 to 4 hours. According to the severity of the disease, each patient received 1 to 4 times of artificial liver support therapy.

2.3 | Observation indicators

The main biochemical indicators were measured before and after treatment, included alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), direct bilirubin (DBIL), albumin (ALB), globulin (GLO), prothrombin activity (PTA), international normalized ratio (INR), creatinine (Cr), urea nitrogen (Urea), white blood cells (WBC), hemoglobin (HGB), platelets (PLT), K^+, Na^+, and Cl^-; and TBIL at 24 and 72 hours after treatment. The second evaluation indexes included the liver transplant-free survival at 28-days after treatment between PE group and DPMAS+PE group. The rates of decline of TBIL immediately after treatment and the rates of decrease in TBIL at 24 and 72 hours after treatment were calculated. The calculation formula were as follows: the immediate decline rate after treatment = [(value before treatment − value immediately after treatment)/value before treatment] × 100%; the decline rate at 24/72 hours after treatment = [(value before treatment − value at 24 or 72 hours after treatment)/value before treatment] × 100%. The severity of the disease was assessed by the Model for End-Stage Liver Disease (MELD) score.[16]

2.4 | Statistical analysis

The data were presented as mean ± SD, median, and percentage based on data characteristics. For the measurement data with normal distribution, the paired sample *t* test was used for comparison within the group, and the independent sample *t* test was used for comparison between groups. For the measurement

data with non-normal distribution, Wilcoxon rank sum test for paired sample comparison was used for comparison within the group, and independent sample Mann-Whitney U rank sum test was used for comparison between groups. The comparison of the rates of count data was performed using the χ^2 test. The survival analysis was tested by Kaplan-Meier method and log-rant test. Statistical analysis was performed using SPSS 24.0 software (SPSS Inc., Chicago, Illinois), and $P < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | General characteristics of the patients

The baseline data for the patients are shown in Table 1. There were no statistically significant differences in disease severity (MELD score) between the 131 enrolled patients and the 13 excluded patients (24.1 ± 5.9 vs 24.7 ± 4.3, $P = 0.351$). Among the 77 patients in the PE group, with an average age of 43.8 years. Among the 54 patients in the DPMAS+PE group, with an average age of 47.6 years. There were no significant differences in age, gender (male, 70.1% vs 70.4%), number of treatments per patient and severity (1.6 ± 0.8 vs 1.5 ± 1.0) of disease between the two groups ($P > 0.05$).

3.2 | Changes in serum biochemical parameters before and after treatment in PE group and DPMAS+PE group

The changes of biochemical indicators before and after treatment were similar in PE group and DPMAS+PE group (Table 2). After treatment, the ALT, AST, TBIL, DBIL, ALB, and GLO were significantly lower than those before treatment in the two groups, and the difference was statistically significant ($P < 0.05$). In the two groups, PTA was significantly increased after treatment ($P < 0.05$), and INR was significantly lower than that before treatment ($P < 0.05$). There was no significant difference in Cr and Urea before and after treatment ($P > 0.05$) in the two groups.

3.3 | Comparison of immediate decline rates in serum biochemical parameters after treatment between PE group and DPMAS+PE group

After treatment, the decrease rates of TBIL and DBIL in DPMAS +PE group were significantly higher than those in PE group (52.3 ± 9.4% vs 42.3 ± 7.2%, 48.6 ± 11.7% vs 41.2 ± 8.2%, $P < 0.05$). There were no significant differences in the decrease rates of ALT, AST, ALB, GLO, PTA, and INR between PE group and DPMAS+PE group ($P > 0.05$) (Table 3).

3.4 | Changes in total bilirubin at 24 hours and 72 hours after treatment in PE and DPMAS+PE groups

In the two groups, the TBIL level decreased significantly after treatment compared with that before treatment, but rebounded

TABLE 1 Comparison of the patient baseline data before treatment between PE group and DPMAS+PE group

	PE group (77 cases)	DPMAS+PE group (54 cases)	P value
Treatments per patient	1.6 ± 0.8	1.5 ± 1.0	0.482
Age (years)	43.8 ± 14.2	47.6 ± 11.5	0.131
Male (n, %)	54(70.1)	38(70.4)	0.966
ALT (U/L)	58.4(39.4, 153.8)	83.1(31.9, 140.4)	0.651
AST (U/L)	104.0(65.2, 158.8)	112.1(82.0, 185.6)	0.241
TBIL (μmol/L)	419.6 ± 151.0	447.7 ± 168.9	0.350
DBIL (μmol/L)	294.7 ± 106.9	330.2 ± 121.0	0.107
Albumin (g/L)	30.9 ± 4.4	30.0 ± 5.0	0.291
globulin (g/L)	24.9 ± 6.1	23.9 ± 7.6	0.487
Creatinine (μmol/L)	55.9 ± 23.4	52.6 ± 18.0	0.485
Urea (mmol/L)	5.5 ± 3.4	5.7 ± 2.7	0.731
PTA (%)	31.6 ± 7.9	29.5 ± 9.3	0.262
INR	2.4 ± 0.5	2.6 ± 0.8	0.240
WBC (×10^9/L)	4.8(3.4, 6.9)	6.3(3.8, 8.1)	0.261
HGB (g/L)	99.2 ± 24.2	101.5 ± 26.3	0.702
PLT (×10^9/L)	71.0(47.3, 112)	107.0(50.0, 155.0)	0.288
K^+ (mmol/L)	3.5 ± 0.6	3.6 ± 0.6	0.643
Na^+ (mmol/L)	136.0 ± 3.9	135.5 ± 3.9	0.579
Cl^- (mmol/L)	99.3 ± 4.2	98.7 ± 4.9	0.761
MELD score	24.3 ± 5.4	23.8 ± 6.2	0.753
Stage of liver failure			0.652
Early stage	41(53.2%)	29(53.7%)	
Intermediate stage	33(42.9%)	21(38.9%)	
Advanced stage	3(3.9%)	4(7.4%)	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBIL, direct bilirubin; HGB: hemoglobin; INR, international normalized ratio; MELD, model end-stage liver disease; PLT: platelets; PTA, prothrombin activity; TBIL, total bilirubin; WBC, white blood cells. P-values are acquired by Chi-square test, t test or Mann-Whitney U rank sum test.

rapidly after 24 hours of treatment. During the treatment period of 24 to 72 hours, bilirubin showed a slow upward trend. The TBIL levels immediately after treatment, and at 24 and 72 hours after treatment were markedly decreased compared with those before treatment, and the differences were statistically significant (P < 0.05) (Figure 1). The TBIL decline rates at 24 and 72 hours after treatment were significantly larger in DPMAS+PE group than in PE group (24.2 ± 10.0% vs 13.5 ± 13.0%, P < 0.05; 24.8 ± 13.1% vs 14.9 ± 14.9%, P < 0.05) (Figure 2).

3.5 | Comparison of liver transplantation free hospital survival at 28-days after treatment between PE group and DPMAS+PE group

The 28-days liver transplantation free hospital survival was 62.3% and 72.2% in PE and DPMAS+PE groups (P = 0.146; Figure 3(A)). Furthermore, there were no significant differences in the 28-days survival between PE group and DPMAS+PE group in the early stage (80.5% vs 82.8%, P = 0.832; Figure 3B). The 28-days survival rates were significantly higher in DPMAS+PE group than that in PE group (57.4% vs 41.7%, P = 0.043) in the intermediate-advanced stage (Figure 3C).

3.6 | Adverse effects

There were no serious adverse reactions related to DPMAS+PE treatment and PE treatment throughout the study.

4 | DISCUSSION

The main finding of this study is that in patients with HBV-ACLF, both PE and DPMAS+PE effectively reduced TBIL levels, but the decline rates of TBIL immediately after treatment, at 24 and 72 hours after treatment in DPMAS+PE group were significantly larger than those in PE group. At the same time, the INR was improved after treatment in both groups. Accordingly, DPMAS+PE improve the 28-days liver transplantation free hospital survival rates in HBV-ACL patients with intermediate-advanced stage. Therefore, DPMAS+PE may be an available ALSS treatment for HBV-

TABLE 2 Changes in serum biochemical parameters before and after treatment in PE group and DPMAS+PE group

|	PE group (n = 77)			DPMAS+PE group (n = 54)		
	Before treatment	After treatment	P value	Before treatment	After treatment	P value
ALT (U/L)	58.4 (39.4153.8)	38.9 (24.4,78.1)	0.000	83.1(31.9140.4)	50.7 (28.8,78.9)	0.000
AST (U/L)	104.0 (65.2158.8)	57.9 (40.3, 90.5)	0.000	112.1(82.0,185.6)	70.7 (50.8114.3)	0.000
TBIL(μmol/L)	419.6 ± 151.0	242.4 ± 92.7	0.000	447.7 ± 168.9	212.8 ± 87.1	0.000
DBIL(μmol/L)	294.7 ± 106.9	171.3 ± 69.2	0.000	330.2 ± 121.0	166.6 ± 68.5	0.000
ALB(g/L)	30.9 ± 4.4	28.6 ± 3.1	0.000	30.0 ± 5.0	26.2 ± 5.0	0.000
GLO(g/L)	24.9 ± 6.1	22.3 ± 3.5	0.000	23.9 ± 7.6	21.1 ± 5.1	0.000
PTA (%)	31.6 ± 7.9	37.8 ± 9.4	0.000	29.5 ± 9.3	33.3 ± 11.4	0.011
INR	2.4 ± 0.5	2.1 ± 0.4	0.000	2.6 ± 0.8	2.4 ± 0.7	0.029
Cr (μmol/L)	55.9 ± 23.4	53.3 ± 22.3	0.404	52.6 ± 18.0	51.8 ± 25.5	0.309
Urea (mmol/L)	5.5 ± 3.4	5.4 ± 3.7	0.421	5.7 ± 2.7	6.1 ± 3.5	0.197

Abbreviations: ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, Creatinine; DBIL, direct bilirubin; GLO, globulin; INR, international normalized ratio; TBIL, total bilirubin; PTA, prothrombin activity. P-values are acquired by paired sample t test or Wilcoxon rank sum test.

TABLE 3 Comparison of decline rates of liver function and coagulation indexes after treatment between PE group and DPMAS+PE group

|	PE group (n = 77)	DPMAS+PE group (n = 54)	P value
ALT (%)	37.3 (29.6, 48.2)	34.1 (22.2, 41.8)	0.135
AST (%)	41.4 ± 11.2	36.8 ± 17.1	0.086
TBIL (%)	42.3 ± 7.2	52.3 ± 9.4	0.000
DBIL (%)	41.2 ± 8.2	48.6 ± 11.7	0.001
ALB (%)	7.8 (0.2, 11.9)	9.8 (1.0, 14.8)	0.108
GLO (%)	13.4 (7.8, 20.8)	9.2 (−0.7, 18.8)	0.204
PTA (%)	−21.1 (−27.5, −12.9)	−19.4 (−21.3, −11.6)	0.406
INR (%)	12.9 (8.0, 19.7)	11.2 (7.2, 18.2)	0.803

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBIL, direct bilirubin; HBG: hemoglobin; INR, international normalized ratio; MELD, model end-stage liver disease; PLT: platelets; PTA, prothrombin activity; TBIL, total bilirubin; WBC, white blood cells. *P*-values are acquired by *t* test or Mann-Whitney U rank sum test.
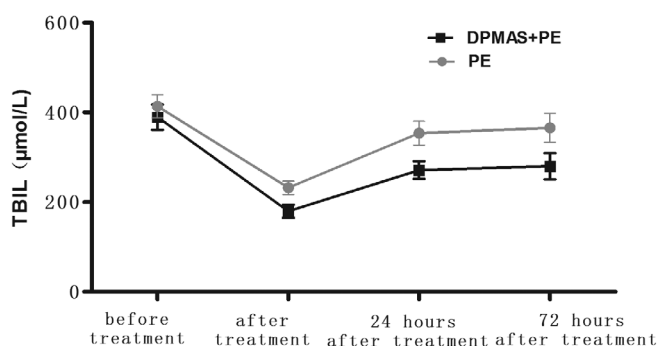

FIGURE 1 Changes in total bilirubin before and after treatment in the DPMAS+PE group and PE group

ACLF, and save the PE volume by 50%, which helps to overcome plasma shortage.

The detoxification function of the liver in patients with ACLF is significantly reduced, and a large amount of toxic substances accumulate in the body, including various water-soluble toxins, protein-bound toxins and metabolites, which seriously affect the regeneration and function recovery of the
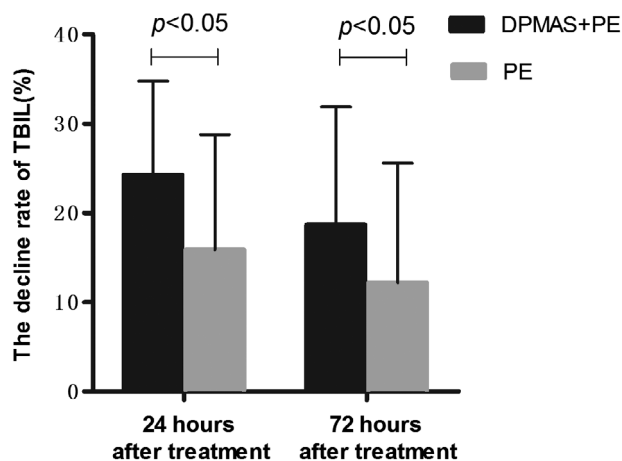
FIGURE 2 Comparison of the decline rates of total bilirubin (TBIL) at 24 and 72 hours after treatment between the DPMAS+PE group and PE group
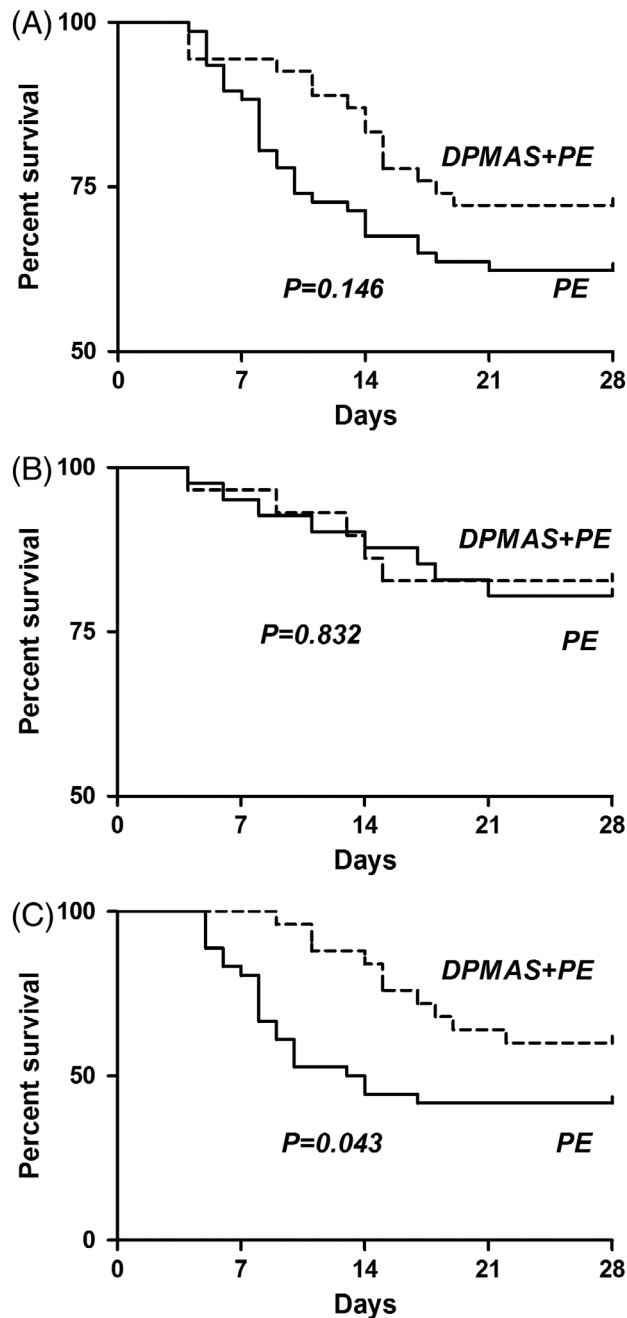
FIGURE 3 Comparison of liver transplantation free hospital survival at 28-days after treatment between PE group and DPMAS+PE group. (A)The included patients. (B) The early stage patients; (C) The intermediate-advanced stage patients

liver cells. As a few important organs can be involved simultaneously, multi-organ dysfunction can occur, resulting in high mortality and extremely poor prognosis.[17,18] Although PE cannot directly improve the synthesis and detoxification functions of the liver, it can eliminate the medium and small molecular metabolic toxins and macromolecules such as proteins and immune complexes in the body, and at the same time it can supplement the essential substances such as albumin and coagulation factors that are lacking in the body, thus it can replace some functions of the liver.[19] A randomized controlled trial has shown that a large amount of PE can

improve the survival of the patients with acute liver failure.[20] A similar study has indicated that PE can improve the liver function in patients with ACLF and prognosis of the patients to some extent as well.[7] Consistent with the results of previous studies, the present study showed that both DPMAS+PE and PE were effective in reducing ALT, AST, TBIL, and DBIL levels in patients with ACLF.

Due to the inadequate supply of plasma, an absolute use of the fresh frozen plasma is limited as a replacement solution for PE treatment. DPMAS uses the plasma separator to separate plasma successively, and the separated plasma is continuously adsorbed by two adsorption columns of neutral macroporous adsorption resin (HA330-II) and ion exchange resin (BS330), and is then returned to the body. It offers an efficient method to fully and constantly remove the medium- and macro-molecules and protein-bound toxins, while specifically eliminating the bilirubin, without need to supplement plasma or replacement solution during treatment. In the study, the clearance rate of TBIL in DPMAS+PE group was significantly higher than that in PE group. The TBIL in patients with ACLF has different degrees of "rebound" after ALSS treatment, which is related to the fact that the underlying lesions such as massive necrosis and cholestasis of hepatocytes continue to exist and bilirubin is persistently released into the blood. Studies have shown the bilirubin rebound after ALSS treatment is negatively correlated with prognosis, that is, the higher the rebound rate, the worse the prognosis.[21] The results showed the decline rates of TBIL at 24 and 72 hours after treatment were significantly higher in DPMAS+PE group than in PE group. DPMAS+PE remove the accumulated metabolites and the substances causing systemic damage such as endotoxin and inflammatory factors. Thus it can create a better environment for liver function recovery. In addition, the treatment time of DPMAS+PE is relatively longer than PE, probably making the patient's bilirubin clearance more complete, and delaying the rebound of bilirubin after treatment as well. And further detailed studies are needed. Accordingly, in our study, the 28-days survival rates were significantly higher in DPMAS+PE group than in PE group in the intermediate-advanced stage. The reason might be that DPMAS+PE provided effective temporary functional support on removal of hepatotoxic metabolites. The transient improvement in biochemical parameters could provide a suitable microenvironment until the donor liver becomes available and to support the failing liver survives spontaneously regenerates.[22]

In addition, the ALSS with a single mode of action may not be sufficient to meet the treatment needs for the patients, so combination of different types of ALSS, using their respective advantages to complement each other, has become a favorable choice.[23,24] Li et al applied a combination of PE, hemoperfusion (HP) and continuous veno-venous hemodialysis filtration (CV-VHDF) in patients with ALF, and the results showed that PE + HP + CVVHDF could effectively remove bilirubin.[25] A study illustrated that PE combined with bilirubin adsorption can effectively remove toxins to improve liver function.[26] Similarly, the results of the present study showed that DPMAS+PE had a significantly higher ability to reduce bilirubin than PE alone.

This study has some limitations. First, it was a retrospective study, but there were no statistically significant differences in the severity of disease between the patients enrolled in the study group and the excluded patients. Second, the number of cases was small. However, since there is no study on the efficacy comparing between DPMAS+PE and full-dose PE, this study has provided some new information on treatment options in patients with HBV-ACLF.

In conclusion, compared with PE treatment alone, DPMAS+PE might more effectively improve the liver function and reduce the rebound of bilirubin in patients with ACLF, and ADPMAS+PE might more effectively improve the 28-days liver transplantation free hospital survival rates in HBV-ACL patients with intermediate- advanced stage. Therefore, DPMAS+PE may be an available ALSS approaches treatment for HBV-ACLF. Further prospective studies are needed to investigate the effect of DPMAS+PE on long-term survival.

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