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Three Artificial Liver Models of Treatment of Acute-on-Chronic Liver Failure

Yanping Xiang, Renhua Li, Jia Cai, Qian Jiang

Department of Infectious Diseases, The First Affiliated Hospital of Chongqing Medical University, Chongqing, People's Republic of China

Correspondence: Renhua Li, Department of Infectious Diseases, The First Affiliated Hospital of Chongqing Medical University, No. 1 Youyi Road, Yuanjiagang, Yuzhong District, Chongqing, 400016, People's Republic of China, Email 854561075@qq.com

Background: This study aimed to investigate clinical efficacy, safety and short-term prognosis of plasma exchange (PE), plasma perfusion combining PE (PP+PE), dual-plasma molecular adsorption system combining PE (DPMAS+PE) in treating acute-on-chronic liver failure (ACLF).

Methods: Two hundred and fourteen ACLF patients admitted to our hospital were included and divided into PE (n = 72), PP+PE (n = 75), DPMAS+PE group (n = 67). Laboratory indexes and MELD scores were collected, and clinical efficacy was compared. Patients' adverse reactions during and 24-h after treatment were collected, and safety was compared. Survival status of patients was followed-up within 90 days, and prognosis was analyzed.

Results: PE, PP+PE and DPMAS+PE significantly reduce TBiL, DBiL, ALT, AST, SA, PT, INR, PCT and CRP levels, and increase PA and PTA levels, compared with pre-treatments ($P < 0.05$). WBC and SCR levels in DPMAS+PE group decreased significantly post-treatment ($P < 0.05$). Na^+ and Cl^- levels in PE and PP+PE group decreased significantly post-treatment ($P < 0.05$). Total adverse reaction incidence in PE, PP+PE, DPMAS+PE group were 38.89%, 22.70%, 17.90%, respectively, with significant differences among three groups ($P < 0.05$). Ninety-day mortality rates of patients in PE, PP+PE, DPMAS+PE group were 41.67%, 34.67%, 20.90%, respectively, with significant differences among three groups ($P < 0.05$).

Conclusion: PE, PP+PE and DPMAS+PE three artificial liver treatment modes can effectively improve liver, kidney and coagulation function of ACLF patients. DPMAS+PE demonstrated better ability to remove endotoxin and inflammatory mediators, showed advantages in reducing ACLF patient mortality within 90 days, and had the least impact on electrolyte post-treatment. Therefore, DPMAS+PE can be used as a better choice for clinical treatment.

Keywords: artificial liver treatment mode, acute-on-chronic liver failure, plasma exchange, plasma perfusion, double plasma molecular adsorption system

Introduction

Acute-on-chronic liver failure (ACLF), as one of the most common types of liver failure in the Asia-Pacific region, is usually caused by the rapid deterioration of symptoms in chronic liver disease patients with relatively stable liver function under various acute injury factors, leading to liver disease syndrome characterized by coagulation disorders, jaundice, hepatic encephalopathy, and other main manifestations.[1] The mortality rates at 28 days and 90 days after ACLF disease are as high as 30% and 58%, respectively.[2,3] Liver transplantation is currently the only potential way to cure ACLF. Research has shown that the one-year survival rate of ACLF patients receiving liver transplantation treatment can reach 80%,[4] but due to the dual limitations of social and economic costs, liver transplantation cannot benefit most ACLF patients. The emergence of non-biological artificial liver (NBAL) has solved this problem. NBAL is a circulatory system that purifies blood through mechanical and biological devices outside the body, which can improve clinical symptoms and indicators, obtain more time for liver cell regeneration, and become a bridge for ACLF patients waiting for liver transplantation.[5,6]

At present, the development of artificial liver treatment models is diversified, and the clinical NBAL treatment models mainly include plasma exchange (PE), plasma perfusion (PP), double plasma molecular adsorption system (DPMAS), plasma diafiltration (PDF), etc. The above treatment modes can be used alone or in combination to

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treat ACLF, achieving the goal of clearing liver endotoxins and reducing liver burden through principles such as adsorption and displacement. The widely used artificial liver treatment models in our hospital mainly include PE, PP+PE, and DPMAS+PE. Currently, the domestic and foreign research mainly focuses on comparing the therapeutic effects of PE and DPMAS+PE treatment, while there is relatively little research on the comparison and short-term prognosis of the three treatment modes mentioned above. This study aimed to compare and analyze the efficacy, safety, and short-term prognosis of the three modes of treatment for ACLF, to evaluate their differences.

Materials and Methods

Patients

This study retrospectively collected ACLF patients admitted to the Infection Department of our hospital from August 2019 to August 2023. Inclusion criteria: ① Age ≥ 18 years old. ② The clinical diagnosis meets the diagnostic criteria for ACLF in the "Guidelines for the Diagnosis and Treatment of Liver Failure (2018 Edition)[7]". ③ During hospitalization, one of the treatment modes for artificial liver disease was PE, PP+PE, or DPMAS+PE. Exclusion criteria: ① Patients with severe heart, brain, kidney diseases, and other causes of active bleeding and DIC. ② Malignant liver tumors and pregnancy status. ③ Allergies to blood products and drugs used in the treatment of artificial liver. ④ Human immunodeficiency virus infected individuals. ⑤ Incomplete clinical data and lost follow-up cases. The patients post the above inclusion and exclusion criteria were divided into 3 groups, including PE group, PP+PE group, and DPMAS+PE group.

Ethical Statement

This study has been approved by the Ethical Committee of the First Affiliated Hospital of Chongqing Medical University (Approval No. 2022-K442). All patients have provided written informed consents and approved this study. This study was performed in accordance with the Helsinki Declaration of 1975, as revised in 2013.

Therapeutic Method

After hospitalization, all three groups of patients underwent liver support treatment on the basis of routine internal medicine therapy (such as protecting the liver and lowering enzymes, reducing jaundice and inflammation, supplementing fluids to maintain water electrolyte balance, and preventing and treating related complications). Before artificial liver treatment, all patients should complete the inspections of blood routine, liver and kidney function, coagulation and other indicators. After confirming that there are no contraindications for treatment, the femoral vein is punctured to establish an extracorporeal circulation channel, and low molecular weight heparin is used for anticoagulation treatment. For the patients in PE group, a plasma separator is used to separate a portion of plasma from the whole blood extracted from the patient's body, and then the plasma is mixed with blood cells in an equal amount of exchange solution before returning it into the body. This process involves exchanging approximately 2000–3000 mL of plasma, with a treatment time of 1.5–3 h. For the patient in PP+PE group, plasma perfusion is performed firstly, which involves adsorbing plasma separated from whole blood through a perfumer. After adsorption, it forms a confluence with the blood and returns to the body, followed by PE treatment. This process involves adsorbing approximately 3000–5500 mL of plasma, replacing approximately 1000–2000 mL of plasma, and treating for 3–4 h. For the patients in DPMAS+PE group, the double adsorption is performed firstly using a disposable hemoperfusion device (Model: HA330-II) and a disposable bilirubin adsorber (Model: BS330), mixed with blood cells, and then infused back, followed by PE treatment. This process involves adsorbing approximately 3000–5200 mL of plasma, replacing approximately 1000–2000 mL of plasma, and treating for 3–4 h. All patients completed treatment under electrocardiogram monitoring and were observed by the bedside for 20 min after treatment.

General Information and Laboratory Indicators Evaluation

The general information of patients based on their hospitalization is collected as baseline, including age, gender, presence or absence of concomitant cirrhosis, etiology, disease stage, and comorbidities of three groups of patients. The number of artificial liver treatments performed by all patients during their hospitalization was statistically analyzed.

The laboratory indicators of patients from three groups 24 h before and 24 h after initial treatment was collected, including total bilirubin (TBil), direct bilirubin (DBil), alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (Alb), prealbumin (PA), serum creatinine (SCr), blood ammonia (SA), red blood cells (RBC), white blood cells (WBC), hemoglobin (Hb), platelets (PLT), prothrombin time (PT), prothrombin activity (PTA), international standardized ratio (INR), fibrinogen (FG), potassium (K^+), sodium (Na^+), chlorine (Cl-), procalcitonin (PCT), C-reactive protein (CRP).

Efficacy Evaluation and Safety Evaluation

According to the improved formula by Kamath et al,[8] the model for end stage liver disease (MELD) score is calculated for all patients before and after treatment. The occurrence of adverse reactions is recorded during and 24 h after treatment in three groups of patients, including rash itching, numbness in the lips/limbs, hypotension, and vasovagal reaction (VVR).

Short Term Prognosis Analysis and Quality Control

Short term prognosis analysis: Starting from the day of discharge and ending 90 days after discharge, the survival status of three groups of patients was followed up by phone to calculate the 90-day mortality rate. Mortality rate (%) = number of deaths in the group within 90 days/total number of deaths in the group × 100%.

To control the quality of data, the data collection process is completed by two master's students conducting a double check, and cases are strictly screened according to inclusion and exclusion criteria. The determination of disease staging and comorbidities in the online data was jointly completed by two current master's students and one resident physician. The diagnostic criteria for disease staging and comorbidities strictly followed relevant guidelines.[7,9,10]

Statistical Methods

This study used SPSS statistical software 27.0 (IBM Corp., Armonk, NY, USA) for data analysis. The quantitative data that conform to a normal distribution are represented by mean ± standard deviation (SD). The paired Student's *t*-test is used for intra-group comparison before and after treatment, and one-way ANOVA is used for inter-group comparison. Measurement data that do not follow a normal distribution are represented by M (P25, P75). The paired rank-sum test is used for intra-group comparison before and after treatment, and multiple independent sample rank-sum test is used for inter-group comparison. Multiple comparisons are conducted using the Bonferroni method. The count data is expressed in percentage (%), and *Chi-square* test is used for inter-group comparison. The difference is statistically significant with $P < 0.05$.

Results

General Information

This study included 214 patients with ACLF, including 164 males and 50 females. According to the artificial liver treatment mode applied, the above patients were divided into three groups: PE group (n = 72), PP+PE group (n = 75), and DPMAS+PE group (n = 67). Comparing general information of patients in three groups, there was no statistically significant difference (Table 1, $P > 0.05$), indicating comparability.

Three Artificial Liver Treatment Modes Improved Liver and Kidney Functions

Compared with pre-treatment, all three artificial liver modes significantly reduced TBil, DBil, ALT, AST, and SA levels in ACLF patients, and significantly increased PA levels in ACLF patients (Table 2, all $P<0.05$). Among them, the changes in SCr levels pre-treatment and post-treatment varied among the three groups of patients, and there was no significant change in SCr levels between pre-treatment and post-treatment in the PE group and the PP+PE group. The SCr level in the DPMAS+PE group significantly decreased post-treatment compared to pre-treatment (Table 2, $P<0.05$).

Table 1 Comparison of General Data Among the Three Groups

Subjects	PE Group (n=72)	PP+PE Group (n=75)	DPMAS+PE Group (n=67)	*F*/ χ^2/*H*	*P*
Age (year)	52.76±13.22	51.08±11.71	53.85±12.43	0.897	0.409
Male/female (n)	57/15	59/16	48/19	1.364	0.506
Combined with liver cirrhosis (n, %)	43 (59.72)	46 (61.33)	37 (55.22)	0.577	0.749
Treatment times (n)	2 (1, 2)	2 (1, 2)	2 (1, 2)	1.941	0.379
Cause of disease (n, %)					
Viral hepatitis	56 (77.78)	59 (78.67)	49 (73.13)	0.684	0.710
Autoimmune hepatitis	4 (5.56)	5 (6.67)	7 (10.45)	1.310	0.519
Medicine	6 (8.33)	5 (6.67)	6 (8.96)	0.276	0.871
Alcohol	6 (8.33)	6 (8.00)	5 (7.46)	0.036	0.982
Staging (n, %)					
Pre-stage	16 (22.22)	14 (18.67)	13 (19.40)	0.318	0.853
Early stage	16 (22.22)	15 (20.00)	21 (31.34)	2.730	0.255
Middle stage	21 (29.17)	34 (45.33)	24 (35.82)	4.173	0.124
Later stage	19 (26.39)	12 (16.00)	9 (13.43)	4.384	0.112
Complications (n, %)					
Hepatic encephalopathy	10 (13.89)	14 (18.67)	8 (11.94)	1.356	0.508
Ascites	28 (38.89)	22 (29.33)	25 (37.31)	1.694	0.429
Primary peritonitis	26 (36.11)	32 (42.67)	26 (38.81)	0.670	0.715

Table 2 Comparison of Liver and Kidney Function Indexes Pre-Treatment and Post-Treatment Among the Three Groups

Indexes	Treatments	PE Group (n=72)	PP+PE Group (n=75)	DPMAS+PE Group (n=67)
TBil (μmol/L)	Pre-treatment	316.26±134.56	374.75±133.61	383.62±130.26
	Post-treatment	215.70±100.59*	205.55±80.74*	197.97±76.34*
DBil (μmol/L)	Pre-treatment	248.02±121.36	299.59±123.60	315.63±122.58
	Post-treatment	155.81±84.61*	143.32±75.56*	139.08±70.98*
ALT (U/L)	Pre-treatment	131.50 (74.00, 372.25)	204.00 (80.00, 450.00)	134.00 (79.00, 348.00)
	Post-treatment	76.00 (43.00, 186.75)*	103.00 (53.00, 216.00)*	77.00 (48.00, 169.00)*
AST (U/L)	Pre-treatment	180.50 (86.00, 292.50)	181.00 (79.00, 381.00)	148.00 (94.00, 296.00)
	Post-treatment	88.50 (52.25, 165.50)*	92.00 (49.00, 181.00)*	80.00 (57.00, 134.00)*
Alb (g/L)	Pre-treatment	32.50 (29.00, 35.00)	33.00 (29.00, 36.00)	32.00 (29.00, 36.00)
	Post-treatment	33.00 (31.00, 35.00)	32.00 (29.00, 34.00)	32.00 (30.00, 36.00)
PA (mg/L)	Pre-treatment	76.50 (64.25, 92.75)	81.00 (67.00, 97.00)	76.00 (58.00, 86.00)
	Post-treatment	90.00 (77.25, 107.75)*	94.00 (81.00, 111.00)*	93.00 (78.00, 117.00)*
SCr (μmol/L)	Pre-treatment	61.50 (48.00, 79.75)	61.00 (45.00, 72.00)	62.00 (50.00, 75.00)
	Post-treatment	59.50 (49.25, 79.25)	60.00 (52.00, 75.00)	58.00 (48.00, 70.00)*
SA (μmol/L)	Pre-treatment	44.25 (33.65, 66.73)	57.20 (40.90, 78.00)	52.00 (40.50, 71.40)
	Post-treatment	42.55 (28.50, 58.68)*	43.60 (28.10, 61.10)*	29.40 (21.70, 48.30)*

Note:*P<0.05 vs Pre-treatment intra-group.

All Artificial Liver Treatment Modes Improve Blood Routine and Coagulation Indicators

The levels of PLT, PT, and INR in the three groups of patients significantly decreased post-treatment compared to those in pre-treatment groups, while the levels of PTA significantly increased (Table 3, all $P < 0.05$). The RBC and Hb levels of patients in the PE group and DPMAS+PE group were significantly lower compared to those in pre-treatment groups (Table 3, all $P < 0.05$). The FG levels of patients in post PE treatment and PP+PE treatment group were significantly

Table 3 Comparison of Blood Routine and Coagulation Indexes of the Three Groups Pre-Treatment and Post-Treatment

Indexes	Treatments	PE Group (n=72)	PP+PE Group (n=75)	DPMAS+PE Group (n=67)
RBC ($\times 10^{12}$/L)	Pre-treatment	3.58 (2.97, 4.03)	3.83 (3.22, 4.22)	3.70 (3.12, 4.19)
	Post-treatment	3.41 (2.68, 3.87)*	3.83 (3.08, 4.23)	3.48 (2.93, 4.03)*
WBC ($\times 10^{9}$/L)	Pre-treatment	6.48 (4.43, 8.44)	6.39 (5.42, 9.00)	6.84 (5.42, 9.25)
	Post-treatment	6.59 (3.96, 8.72)	6.76 (4.72, 9.80)	6.35 (4.55, 8.92)*
Hb (g/L)	Pre-treatment	110.50 (98.00, 132.75)	113.00 (98.00, 129.00)	110.00 (101.00, 126.00)
	Post-treatment	107.50 (92.00, 126.00)*	114.00 (97.00, 126.00)	105.00 (91.00, 121.00)*
PLT ($\times 10^{9}$/L)	Pre-treatment	93.00 (66.75, 132.50)	104.00 (64.00, 156.00)	120.00 (78.00, 157.00)
	Post-treatment	84.50 (72.00, 123.50)*	83.00 (51.00, 130.00)*	100.00 (67.00, 144.00)*
PT (s)	Pre-treatment	22.05 (17.73, 26.95)	21.50 (19.30, 25.90)	20.00 (17.50, 22.90)
	Post-treatment	17.00 (15.80, 18.48)*	18.80 (17.40, 20.70)*	17.60 (16.00, 19.20)*
PTA (%)	Pre-treatment	40.00 (30.00, 59.75)	40.00 (33.00, 50.00)	45.00 (36.00, 54.00)
	Post-treatment	60.00 (53.00, 68.00)*	50.00 (45.00, 58.00)*	56.00 (50.00, 66.00)*
INR	Pre-treatment	1.95 (1.42, 2.52)	1.91 (1.66, 2.36)	1.73 (1.51, 2.15)
	Post-treatment	1.40 (1.28, 1.55)*	1.57 (1.43, 1.76)*	1.47 (1.29, 1.63)*
FG (g/L)	Pre-treatment	1.64 (1.38, 2.29)	1.57 (1.38, 2.04)	1.60 (1.38, 2.10)
	Post-treatment	1.96 (1.53, 2.42)*	1.43 (1.18, 1.73)*	1.63 (1.31, 2.19)

Note: *P<0.05 vs Pre-treatment intra-group.

lower than pre-treatments (Table 3, all $P < 0.05$). The WBC levels of patients in the DPMAS+PE group were significantly lower than pre-treatments (Table 3, all $P < 0.05$).

Three Artificial Liver Treatment Modes Regulated Electrolytes, Inflammatory Markers and MELD Scores

Post treatment, the PCT, CRP levels, and MELD scores of patients in three groups significantly decreased compared to those in pre-treatment groups (Table 4, all $P < 0.05$). Compared with pre-treatment, the levels of Na^+ and Cl^- in patients of PE group and PP+PE group significantly decreased post treatment (Table 4, all $P < 0.05$), while the K^+ levels in patients of the PP+PE group significantly increased post treatment (Table 4, $P < 0.05$).

Table 4 Comparison of Electrolyte and Inflammation Indexes Pre-Treatment and Post-Treatment Among the Three Groups

Indexes	Treatments	PE Group (n=72)	PP+PE Group (n=75)	DPMAS+PE Group (n=67)
K^+ (mmol/L)	Pre-treatment	3.85 (3.60, 4.20)	3.90 (3.50, 4.10)	3.90 (3.50, 4.30)
	Post-treatment	3.80 (3.40, 4.10)	4.00 (3.70, 4.20)*	3.90 (3.60, 4.20)
NA^+ (mmol/L)	Pre-treatment	137.00 (134.00, 139.00)	136.00 (134.00, 139.00)	136.00 (134.00, 137.00)
	Post-treatment	135.00 (132.00, 138.00)*	135.00 (132.00, 137.00)*	135.00 (133.00, 137.00)
CL^- (mmol/L)	Pre-treatment	100.00 (95.00, 103.00)	100.00 (96.00, 104.00)	101.00 (97.00, 104.00)
	Post-treatment	98.00 (93.00, 100.75)*	99.00 (96.00, 102.00)*	100.00 (98.00, 103.00)
PCT (ng/mL)	Pre-treatment	0.50 (0.32, 0.82)	0.54 (0.39, 0.83)	0.48 (0.38, 0.75)
	Post-treatment	0.39 (0.27, 0.57)*	0.40 (0.32, 0.55)*	0.34 (0.25, 0.42)*
CRP (mg/L)	Pre-treatment	12.90 (8.46, 20.14)	12.50 (7.77, 20.30)	14.20 (10.70, 21.10)
	Post-treatment	8.34 (5.43, 14.43)*	7.65 (5.26, 12.00)*	6.30 (4.46, 10.20)*
MELD (scores)	Pre-treatment	25.00 (21.00, 28.00)	26.00 (23.00, 29.00)	25.00 (23.00, 27.00)
	Post-treatment	20.00 (18.00, 22.00)*	21.00 (18.00, 23.00)*	20.00 (18.00, 22.00)*

Note: *P<0.05 vs Pre-treatment intra-group.

Comparison of Differences Between Pre-Treatment Minus Post-Treatment Among Three Modes

To further compare the clinical efficacy of the three artificial liver modes and eliminate the sampling artifacts, this study calculated the differences between pre-treatment and post-treatment for the indicators with significant differences among all three artificial liver modes and analyzed the differences (b value = pre-treatment minus post-treatment) among all three modes. The results showed that the differences (pre-treatment minus post-treatment) for the TBIL, DBIL, SA, PTA, PCT and CRP had significant statistical differences among the three groups (Table 5, all $P < 0.05$).

Comparison of Differences of Pre-Treatment Minus Post-Treatment Between Two Different Modes

The above 6 indicators were further compared by Bonferroni method to clarify which two groups had differences. The results showed that there were significant differences for the differences of pre-treatment minus post-treatment (TBIL, DBIL and PTA) between PE group and PP+PE group (Table 6, $P < 0.05$). There were significant differences for the differences of pre-treatment minus post-treatment (TBIL, DBIL, SA, PCT and CRP) between DPMAS+PE group and PE group (Table 6, $P < 0.05$). There were also significant differences for the differences of pre-treatment minus post-treatment (SA and CRP) between PP+PE group and DPMAS+PE group (Table 6, $P < 0.05$).

Table 5 Comparison of the Difference Between Pre-Treatment and Post-Treatment (B=pre-Treatment Minus Post-Treatment) Among the Three Groups

Indexes	PE Group (n=72)	PP+PE Group (n=75)	DPMAS+PE Group (n=67)	*F/H*	*P*
TBil [b] (μmol/L)	100.56±69.62	169.20±79.43	185.65±75.20	25.699	<0.001
DBil [b] (μmol/L)	92.21±68.61	156.27±69.53	176.55±79.93	25.916	<0.001
ALT [b] (U/L)	56.00 (27.00, 170.50)	88.00 (24.00, 207.00)	66.30 (25.00, 184.00)	0.357	0.836
AST [b] (U/L)	76.50 (25.25, 137.00)	75.00 (28.00, 185.00)	68.00 (31.00, 161.00)	0.131	0.937
PA [b] (mg/L)	−14.00 (−24.00, −4.00)	−15.00 (−31.00, −4.00)	−19.00 (−31.00, −8.00)	3.196	0.202
SA [b] (μmol/L)	6.35 (−11.33, 23.65)	14.50 (−2.10, 0.20)	18.60 (10.20, 32.40)	17.819	<0.001
PLT [b] (×10^9/L)	10.00 (1.25, 17.00)	15.00 (5.00, 28.00)	12.00 (5.00, 24.00)	3.642	0.162
PT [b] (s)	4.25 (1.56, 8.68)	3.10 (0.80, 5.30)	2.70 (0.50, 5.20)	5.872	0.053
PTA [b] (%)	−17.00 (−24.75, −6.00)	−9.00 (−15.00, −3.00)	−12.00 (−18.00, −4.00)	13.277	<0.001
INR [b]	0.45 (0.15, 0.94)	0.33 (0.11, 0.61)	0.28 (0.06, 0.54)	5.027	0.081
PCT [b] (ng/mL)	0.06 (0.01, 0.24)	0.10 (0.01, 0.30)	0.13 (0.08, 0.25)	6.234	0.044
CRP [b] (mg/L)	5.05 (1.67, 6.96)	5.42 (1.51, 9.10)	7.61 (4.53, 10.20)	15.643	<0.001
MELD [b] (scores)	4.00 (3.00, 7.00)	5.00 (4.00, 7.00)	4.00 (3.00, 6.00)	1.413	0.493

Note: [b]value=pre-treatment minus post-treatment for various indexes.

Table 6 Comparison for the Differences of Pre-Treatment Minus Post-Treatment Between Different Artificial Liver Treatment Modes

Indexes	PE vs PP+PE (*P* values)	PE vs DPMAS+PE (*P* values)	PP+PE vs DPMAS+PE (*P* values)
TBil (μmol/L)	<0.001	<0.001	0.578
DBil (μmol/L)	<0.001	<0.001	0.295
SA (μmol/L)	0.201	<0.001	0.042
PTA (%)	0.001	0.088	0.534
PCT (ng/mL)	0.549	0.038	0.677
CRP (mg/L)	0.624	<0.001	0.022

Adverse Reactions of Patients in Three Artificial Liver Treatment Modes

A total of 28 cases of adverse reactions occurred in the PE group (38.89%), 17 cases of adverse reactions occurred in the PP+PE group (22.70%), and 12 cases of adverse reactions occurred in the DPMAS+PE group (17.90%). The statistical results showed that there was a statistically significant difference for the incidence of adverse events among the three groups (Table 7, $P < 0.05$). The *Chi-square* method comparing the differences between two groups showed that there was a significant difference for the incidence of adverse reactions between the PE group and the PP+PE group (Table 7, $\chi^2 = 4.551$, $P = 0.033$). There was significant difference for the incidence of adverse reactions between the PE group and the DPMAS+PE group (Table 7, $\chi^2 = 7.452$, $P = 0.006$). There was not a statistically significant difference for the incidence of adverse reactions between the PP+PE group and the DPMAS+PE group (Table 7, $\chi^2 = 0.493$, $P = 0.483$).

Prognosis Analysis 90 Days Post Treatments

A total of 30 cases (41.67%) died within 90 days in PE group, 26 cases (34.67%) died in PP+PE group, and 14 cases (20.90%) died in DPMAS+PE group (Table 8). The statistical results showed that the mortality rate within 90 days among three groups was significantly different (Table 8, $P < 0.05$). The comparison results between the three groups by Chi-square partition showed that there was no significant difference for 90-day mortality between the PE group and the PP+PE group (Table 8, $\chi^2 = 0.763$, $P = 0.382$) and between the PP+PE group and the DPMAS+PE group (Table 8, $\chi^2 = 3.317$, $P = 0.069$). However, there was significant difference for 90-day mortality between the PE group and the DPMAS+PE group (Table 8, $\chi^2 = 6.921$, $P = 0.009$).

Discussion

ACLF seriously threatens the life safety of patients, with rapid clinical deterioration, high mortality and poor prognosis, which brings heavy burden to families and society, and is regarded as one of the global public health challenges.[11] Because the pathogenesis of ACLF is not completely clear, there is no specific treatment at present. The effect of medical treatment is not optimistic, and liver transplantation is limited in many aspects. NBAL has been recommended by multiple guidelines as an adjuvant treatment for ACLF.[12,13]

The key to the treatment of liver failure is to timely remove toxins from the body and promote the recovery of liver function. PE is one of the important means to treat ACLF. The treatment effect can be achieved by fresh frozen plasma exchange of plasma containing various toxins and pathogenic factors. However, PE cannot effectively remove a large amount of water-soluble toxins distributed in the plasma, and the improvement effect on severe hepatic encephalopathy is

Table 7 Comparison of the Incidence of Adverse Reactions Among the Three Groups (n, %)

Adverse Reactions	PE Group (n=72)	PP+PE Group (n=75)	DPMAS+PE Group (n=67)	χ^2	*P*
Rash pruritus	14 (19.44)	8 (10.67)	4 (5.97)		
Numbness of lips/limbs	9 (12.50)	7 (9.33)	5 (7.46)		
Hypotension	5 (6.94)	2 (2.67)	1 (1.49)		
VVR	0	0	2 (2.99)		
Total	28 (38.89)	17 (22.70)	12 (17.90)	8.747	0.013

Abbreviation: VVR, vasovagal response.

Table 8 Comparison of 90-Day Mortality Among Patients in Three Groups (n, %)

Treatment Modes	Cases	Survival	Death	χ^2	*P*
PE	72	42 (58.33)	30 (41.67)		
PP+PE	75	49 (65.33)	26 (34.67)	7.003	0.030
DPMAS+PE	67	53 (79.10)	14 (20.90)		

poor.[14–16] PE alone requires a large amount of plasma, and the amount of plasma exchanged at a time is about 3000–4000 mL, which greatly limits the development of PE alone treatment in the environment of lack of blood resources. The emergence of combined treatment mode makes up for this defect. PP treatment is to flow the plasma separated from whole blood through a bilirubin adsorption column (BS330) to specifically adsorb bilirubin and a small amount of bile acids.[17] DPMAS uses a resin hemoperfusion device (HA330-II) that can adsorb medium macromolecular toxins on basis of PP. After double adsorption, plasma can increase the clearance rate of various toxins and improve the prognosis of patients.[18,19]

The comparative analysis of the clinical indicators of the three groups before and after treatment showed that the three treatment modes could improve the liver and kidney function and coagulation function of patients to varying degrees and reduce the inflammatory indicators. Further comparison of the differences between pre-treatment and post-treatment of the three groups revealed that the two combined treatment modes were more effective in reducing TBIL and DBIL levels in patients with ACLF than PE treatment alone. Compared with PE and PP+PE treatment, DPMAS+PE treatment has better efficacy in removing SA and CRP, which may be related to two adsorption columns in series, similar to the research results of domestic scholars.[20,21]

Patients with liver failure are often complicated with electrolyte disorders, the most common of which is hyponatremia. Hyponatremia and loss of serum sodium may affect brain function and increase the risk of complications of hepatic encephalopathy.[22,23] The results of this study showed that the levels of Na^+ and Cl^- in PE group and PP+PE group decreased significantly after treatment, while the levels of Na^+ and Cl^- in DPMAS+PE group did not change significantly pre-treatment and post-treatment. It can be seen that DPMAS+PE group has the least influence on electrolyte levels of patients with ACLF pre-treatment and post-treatment and can better maintain the balance of Na^+ and Cl^- levels. According to the ammonia poisoning theory, SA is considered the core of the pathogenesis of hepatic encephalopathy, and significantly elevated SA can induce hepatic encephalopathy by reaching the central nervous system through the blood–brain barrier. Foreign scholars reported that,[24,25] the high level of SA is closely related to the high 28-day mortality of patients with ACLF. This study showed that the ability of removing SA in DPMAS+PE group was stronger than that in PE and PP+PE groups, indicating that this mode is more suitable for patients with preoperative electrolyte disorders and hyperammonemia.

Additionally, the inflammatory response mediated by immune imbalance is considered the initiating factor of ACLF, and cytokines play an important role in this link.[26] Cytokines are strengthened when liver tissue is damaged, which leads to the increase of CRP level.[27] This study showed that the three treatment modes can significantly reduce the CRP level. Further comparison of the difference showed that DPMAS+PE has better improvement effect on CRP than the other two modes. Zhu et al[28] found that the increased WBC level may be related to massive necrosis of hepatocytes and endotoxemia, which can increase the risk of death in patients with ACLF. This study showed that only the DPMAS +PE group had significantly decreased WBC levels after treatment. Obviously, DPMAS+PE combination therapy can more effectively control the "inflammatory storm" in the body of patients with ACLF, reduce the expression level of inflammatory mediators in the body, thereby delaying or even blocking the progression of liver failure.

The combined mode not only reduces the amount of plasma but also reduces the incidence of adverse reactions during artificial liver treatment. However, it is worth noting that this study found a new complication in the treatment of DPMAS+PE in the past 2 years. The vasovagal response (VVR) is an abnormal autonomic imbalance mediated by the vagus nerve, which can trigger progressive heart rate reduction and blood pressure reduction.[28] VVR is a rare complication in artificial liver treatment. In this study, among 67 patients with ACLF, VVR occurred twice (2.99%), accompanied by dizziness, nausea, vomiting, sweating and other symptoms in addition to the reduction of heart rate and blood pressure. In the past, VVR was more common in blood donation,[29] spinal injection,[30] percutaneous coronary intervention.[31] In this study, two patients with ACLF who developed VVR gradually returned to normal within 30 min after slowing down the blood flow velocity and intravenous injection of atropine. At present, the occurrence mechanism and treatment process of artificial liver-related VVR are still lack of normative guidelines. Medical staff should pay attention to early recognition and treatment in the treatment process to prevent serious consequences.

This study also demonstrated a few limitations. First, this study is a single-center retrospective study, with insufficient sample size and lack of long-term prognosis evaluation data. Therefore, a multi-center prospective study with large samples can be carried out for further verification in the following studies. Second, all patients in this study were followed up for less 90 days, therefore, some results need to be confirmed with further investigations.

Conclusion

PE, PP+PE and DPMAS+PE can effectively reduce liver damage, reduce MELD score and improve prognosis. The combined artificial liver mode not only improved the safety but also significantly reduced the short-term mortality of patients with ACLF. DPMAS+PE had better clinical effect in adsorbing inflammatory factors, clearing SA and SCR than PE or PP+PE alone, and had less impact on electrolyte. At the same time, the incidence of adverse reactions and 90-day mortality were also significantly lower than the former two, showing better clinical application value.

Data Sharing Statement

All data are available from the corresponding author.

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Disclosure

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