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ORIGINAL PAPER

Efficacy of Various Combined Blood Purification Techniques for Treating Patients with Non-viral Acute Liver Failure

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Abstract We sought to study the clinical efficacy of various combined blood purification techniques in patients with non-viral acute liver failure complicated by multiple organ dysfunction syndrome (MODS). For this purpose, 19 patients diagnosed of mid- or late-stage liver failure with MODS score-4 were randomly divided into 3 treatment groups of PE+HP+CVVHDF, PE+CVVHDF, and HP+CVVHDF, respectively. Pre- and post-treatment heart rate (HR), mean arterial pressure (MAP), arterial blood gases (pH, PaO_2, and $PaCO_2$), hepatic function, platelet count, and blood coagulation were determined. The data show significant improvement in HR, MAP, PaO_2/FiO_2, total bilirubin (TBIL), and alanine aminotransferase (ALT) levels after treatment ($P < 0.05$). TBIL decreased more significantly after treatment in PE+CVVHDF and PE+HP+CVVHDF groups ($P < 0.01$). Significant improvement in prothrombin time and albumin was observed only in PE+CVVHDF and PE+HP+CVVHDF groups ($P < 0.05$). The decrease of TBIL and improvement of PaO_2/FiO_2 ratio were more pronounced in PE+HP+CVVHDF than in HP+CVVHDF group ($P < 0.05$). To conclude, liver function was relatively improved by all the three combined blood purification techniques used; however, PE+HP+CVVHDF approach was found more efficient in the removal of toxic metabolites, especially bilirubin. The data suggest that the combined blood purification techniques used were effective and involved minor side effects.

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Introduction

Acute liver failure (ALF) is caused by both viral and non-viral hepatitis including drug intoxication, poisoning, hypoxia, postpartum hepatic failure, etc. all of which can lead to severe metabolic disorders and accumulation of toxic substances. The continuous accumulation of endotoxins and inflammatory mediators, and their persistent release into the blood circulation, in turn, cause further damage to the liver and inhibit regeneration of liver cells, thereby setting off a detrimental circle. Despite the use of multiple therapeutic strategies, such as hepatoprotective therapy, control of jaundice, supportive treatment, etc., ALF continues to be a major therapeutic challenge in the field due to its high mortality rate of up to 70 % [1]. Nonbiological artificial liver support systems, as one type of blood purification therapy, temporarily and partially compensate liver function by detoxifying and supplementing bioactive agents that help in liver cell regeneration and functional recovery. While the efficacy of single blood purification treatment is limited, combined purification therapy with multiple methods has become the focus for current research on nonbiological artificial liver therapy. Herein, we compared and determined the clinical efficacy of three combination therapies including: (1) plasma exchange (PE), hemoperfusion (HP), and continuous veno-venous hemodiafiltration (CVVHDF); (2) PE and CVVHDF; and (3) HP and CVVHDF in order to find a more promising and cost-effective blood purification treatment for patients with non-viral ALF.

Materials and Methods

Patients

During January 2007 to December 2011, 19 patients, with severe liver failure complicated with multiple organ dysfunction syndrome (MODS) (MODS score of 4, serum bilirubin >240 μmol/L) and admitted to our Hospital's Critical Care Department, were enrolled in the study following their written informed consent and approval of study protocol by the institutional ethics committee. Among these patients, 13 were male and 6 were female with a mean age of 43.7 ± 13.91 (range 20–82) years, having mean value of APACHEII score of 24.2 ± 5.5 and mean SOFA score of 13.34 ± 3.46. Prior diseases or morbid conditions included cardiac surgery in one patient, drug toxicity in seven patients, postpartum in four patients, mushroom poisoning in one patient, and severe infection in six patients. Serious complications in patients included renal dysfunction in 15 cases, hepatoencephalopathy in 11 cases, gastrointestinal bleeding in 14 cases, and coagulation abnormalities in 19 cases.

Artificial Liver Support Treatment

In addition to general treatment, 19 patients were randomly divided into 3 groups including PE+HP+CVVHDF group, PE+CVVHDF group, and HP+CVVHDF group. In PE+HP+CVVHDF group, a temporary access was established through femoral vein or internal jugular vein catheterization. PE was implemented at bedside using standard plasma filters (Gambro PF 2000N, Switzerland). A total volume of 1,500–3,000 mL of fresh plasma was exchanged in 2–3 h for each session at a blood flow of 80–120 mL/min and exchange rate of 25–30 mL/min. HP was performed after each session of PE using a neutral macroporous high molecular resin (HA33-II, Zhuhai Lizhu Medical Bio-Material Co. Ltd., China) for 2–3 h until the adsorption capacity of HP reached saturation. Patients received CVVHDF after the completion of HP. In PE+CVVHDF group, PE and CVVHDF were performed as tandem procedures. In HP+CVVHDF group, HP procedure was combined with CVVHDF. The interval between PE and HP was 1–2 days for a total of 2–5 times of therapy. Thus, 19 patients received a total of 51 sessions of therapies including 13 sessions of PE+HP+CVVHDF, 15 sessions of PE+CVVHDF, and 23 sessions of HP+CVVHDF.

Monitor Proceedings

Patients were monitored continuously for consciousness, heart rate (HR), mean arterial pressure (MAP), and transcutaneous oxygen saturation. Hepatic and renal function, arterial blood gases (pH, PaO_2, and $PaCO_2$), blood count, electrolytes, and blood coagulation were tested and recorded before and after each therapy.

Statistical Analysis

Statistical analysis of the data was performed using SPSS 12.0 software. Data were presented as mean ± standard deviation. Comparison between groups was performed by one-way ANOVA, and $P < 0.05$ was considered statistically significant.

Results

Patients' Characteristics

There was no significant difference found regarding age, SOFA score, and total time of treatment of patients in three groups ($P > 0.05$; Table 1).

Changes in Hemodynamics, Blood Oxygenation Level, and Platelet Counts

The data regarding hemodynamics, blood oxygen, and platelet counts are summarized in Table 2. In this regard, HR, MAP, and index of arterial oxygenation efficiency i.e., the ratio of partial pressure of arterial O_2 to the fraction of inspired O_2 (PaO_2/FiO_2) significantly increased ($P < 0.05$) after the therapy in each group. However, a significant increase ($P < 0.01$) was observed in PE+HP+CVVHDF and PE+CVVHDF groups. Additionally, PaO_2/FiO_2 ratio was significantly improved ($P < 0.05$) in PE+HP+CVVHDF

Table 1 Age, SOFA score, and time of therapy of the patients

Group	Age (years)	SOFA score	Time of therapy (h)
HP+CVVHDF ($N = 23$)	44.66 ± 14.91	12.64 ± 2.95	18.79 ± 5.63
PE+CVVHDF ($N = 15$)	42.12 ± 14.15	13.35 ± 3.12	22.14 ± 6.10
PE+HP+CVVHDF ($N = 13$)	39.78 ± 12.75	14.04 ± 3.08	19.92 ± 5.25

SOFA score Sepsis-Related Organ Failure Assessment Score, *HP+CVVHDF* hemoperfusion plus continuous veno-venous hemodiafiltration, *PE+CVVHDF* plasma exchange plus continuous veno-venous hemodiafiltration, *PE+HP+CVVHDF* plasma exchange plus hemoperfusion plus continuous veno-venous hemodiafiltration

Table 2 Changes in hemodynamics, blood oxygenation level, and platelet count before and after therapy

Group	HR	MAP	PaO_2/FiO_2	PLT ($\times 10^9$/L)
HP+CVVHDF ($N = 23$)				
Pre-therapy	137 ± 20.92	79.44 ± 14.70	239 ± 47.57	77.85 ± 35.45
Post-therapy	117 ± 23.45[a]	90.53 ± 11.17[a]	280 ± 52.01[a]	70.82 ± 34.78
PE+CVVHDF ($N = 15$)				
Pre-therapy	136 ± 21.17	79.22 ± 13.43	236 ± 48.64	82.55 ± 40.38
Post-therapy	118 ± 24.01[a]	91.01 ± 12.76[a]	291 ± 54.31[b]	75.36 ± 39.52
PE+HP+CVVHDF ($N = 13$)				
Pre-therapy	135 ± 23.66	80.63 ± 12.88	228 ± 50.49	81.98 ± 44.71
Post-therapy	116 ± 22.18[a]	91.13 ± 10.92[a]	310 ± 60.72[bcd]	72.01 ± 38.92

HR heart rate, *MAP* mean arterial pressure, *PaO_2/FiO_2* an index of arterial oxygenation efficiency that corresponds to ratio of partial pressure of arterial O_2 to the fraction of inspired O_2, *PLT ($\times 10^9$/L)* platelet count

[a] Post- versus pre-therapy $P < 0.05$

[b] Post- versus pre-therapy $P < 0.01$

[c] PE+HP+CVVHDF group versus HP+CVVHDF group $P < 0.05$

[d] PE+HP+CVVHDF group versus PE+CVVHDF group $P < 0.05$

group as compared with HP+CVVHDF group. No significant changes in platelet count were observed in these groups ($P > 0.05$).

Changes in Blood Coagulation and Liver Functions

As shown in Table 3, total bilirubin (TBIL) and alanine aminotransferase (ALT) were found significantly decreased after the therapy in all groups ($P < 0.05$). A more significant decrease ($P < 0.01$) was observed in PE+CVVHDF group as compared with PE+HP+CVVHDF group. TBIL level was lower ($P < 0.05$) in PE+HP+CVVHDF group as compared with HP+CVVHDF group. A significant improvement ($P < 0.05$) was obsereved in prothrombin time (PT) and albumin (ALB) levels in PE+CVVHDF and PE+HP+CVVHDF groups. Among the 19 patients treated by artificial hepatic support therapy, 14 patients survived and 5 patients died; hence a mortality rate of 26.3 % and a survival rate of 73.7 %.

Discussion

The management of patients with ALF using various combined blood purification therapies plays a critical role in lowering serum bilirubin, eliminating or reducing accumulation of toxins, and improving patients' health status. As previously reported [2], a survival rate of 80–90 % was found in patients receiving treatment early in the course of the disease, while 60–70 % survival rate was observed in patients that were treated in the mid-stage; however, the survival rate was not more than 20 % in

Table 3 Changes in blood coagulation and liver function before and after therapy

Group	PT (S)	TBIL	ALT	ALB
HP+CVVHDF ($N = 23$)				
Pre-therapy	25.83 ± 14.67	349.75 ± 152.98	487.56 ± 267.51	26.54 ± 5.37
Post-therapy	22.57 ± 12.07	314.84 ± 143.11[a]	197.05 ± 89.49[b]	27.71 ± 5.40
PE+CVVHDF ($N = 15$)				
Pre-therapy	26.51 ± 15.66	354.23 ± 141.96	515.66 ± 270.56	25.11 ± 4.54
Post-therapy	18.84 ± 11.17[b]	284.22 ± 134.15[b]	181.60 ± 81.15[b]	29.05 ± 4.32[a]
PE+HP+CVVHDF ($N = 13$)				
Pre-therapy	27.86 ± 15.04	362.23 ± 161.90	498.74 ± 285.93	24.97 ± 5.23
Post-therapy	19.85 ± 11.64[b]	265.92 ± 147.69[bc]	176.42 ± 78.81[b]	28.58 ± 4.84[a]

PT prothrombin time, *TBIL* total bilirubin, *ALT* alanine transaminase, *ALB* albumin

[a] Post- versus pre-therapy $P < 0.05$

[b] Post- versus pre-therapy $P < 0.01$

[c] PE+HP+CVVHDF group versus HP+CVVHDF group $P < 0.05$

patients treated at the late-stage of the disease. Ye et al. [3] reported the survival rate of 48.3 % in patients with severe chronic hepatitis B treated by PE combined with continuous veno-venous hemofiltration (CVVHF). In the study of the management of patients with ALF associated with MODS, He et al. [4] reported a survival rate of 45.5 % in patients treated with plasma filtration adsorption combined with CVVHF. Similar, another study [5] reported a survival rate of 42.5% in patients treated by PE combined with CVVHDF.

In the present study, all patients were diagnosed as mid- or late-stage liver failure cases (prothrombin activity $\leq$ 30 %) according to the diagnostic and treatment guidelines for liver failure [6], and were classified as most severe liver failure based on MODS scoring system (MODS score of 4, serum bilirubin $\geq$ 240 μmol/L). These patients were treated with three different combined blood purification therapies, and 12 out of the 19 patients survived and the survival rate (73.7 %) was significantly higher than the rates reported by the previous studies [7–10]. The difference in the therapeutic results is due likely to the etiology of the disease. Notably, the patients in previous studies suffered from liver failure caused by viral hepatitis, whereas we herein studied non-viral ALF patients. Further, in this regard, non-viral liver disease is easier to treat as compared to viral liver disease. Once the cause of liver damage is identified and eliminated, impaired hepatocytes can be repaired and allowed to regenerate until the liver function is gradually restored; however, serious metabolic disorder and accumulation of toxic metabolites caused by severe injury to hepatocytes can lead to the accumulation and continuous release of large amount of endotoxins and inflammatory mediators. Combined therapy by using different blood purification techniques has been proved to be effective for improving the prognosis of the patients with non-viral ALF.

In case of liver failure, endogenous toxic metabolites, such as bilirubin, cholic acid, albumin-binding macromolecules, and circulating immune complexes, can be removed by PE; meanwhile, the use of fresh frozen plasma as a replacement fluid in PE is also important in order to replenish the deficient coagulation factors to improve the coagulation function and provide essential metabolic factors including albumin, opsonin, immunoglobulin, and other bioactive substances. In addition, PE can also improve and restore the humoral and cellular immune responses in patients to inhibit the progression of the disease [11]. However, using PE alone cannot efficiently remove the medium and small toxins which can easily penetrate blood vessel wall and widely infiltrate in the tissue. HP with resin adsorption can eliminate toxins as well as aromatic amino acids, phenol, indole, short-chain fatty acids, etc. HA330-II resin has the relative specificity for bilirubin, cholic acids, and cytokines. Besides, the resin adsorption can effectively remove the protein-bound toxins and toxic factors inhibiting liver regeneration [12]. CVVHDF is effective in removal of medium-sized molecules, ammonia, and other toxins, such as false neurotransmitters, free fatty acids, mercaptans, and aromatic amino acids, which increases cAMP level in cerebrospinal fluid, improves energy metabolism in the brain, and alleviates hepatic encephalopathy. As well, CVVHDF can precisely control the fluid volume by continuously and slowly removing solutes and fluid from the body, regulating fluid, electrolyte, and acid–base balance and reducing the incidence of cerebral edema in ALF patients.

However, there are few caveats involved that warrant caution while interpreting results of the study. First, the sample size is relatively small; therefore, further large-size multi-center studies will be required to verify these findings. Next, as a previous study [13] reported that the use of Molecular Absorbent Recirculating System could significantly improve patients' survival, a study comparing other methods with this technique would be required to assess the most effective treatment for non-viral liver failure.

In conclusion, the data from this study of the efficacy of three different combination therapies used for liver support in non-viral ALF patients show significant improvement of TBIL, ALT, PT, and ALB in PE+HP+CVVHDF and PE+CVVHDF therapy groups. Besides, TBIL reduction was more remarkable in PE+HP+CVVHDF group compared with other groups, indicating that this combinatorial approach was more effective for removing toxins/metabolites and maintaining homeostasis. Also, the combinatorial approach was more effective than solitary methods. Nonetheless, further studies will be required to validate these preliminary findings.

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