

High-volume hemofiltration plus hemoperfusion for hyperlipidemic severe acute pancreatitis: a controlled pilot study

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Ann Saudi Med 2015; 35(5): 352-358

DOI: 10.5144/0256-4947.2015.352

BACKGROUND AND OBJECTIVES: The evidence for high-volume hemofiltration plus hemoperfusion (HVHF&HP) for hyperlipidemic severe acute pancreatitis (HL-SAP) is anecdotal. The purpose of our study was to evaluate the efficacy of HVHF&HP for HL-SAP in a prospective controlled study.

DESIGN AND SETTING: Prospective controlled pilot study between May 2010 and May 2013 in a hospital intensive care unit.

PATIENTS AND METHODS: HL-SAP patients chose conventional treatment alone (the control group) or conventional treatment combined with the experimental protocol (the HVHF&HP group) and were prospectively followed in our hospital. APACHE II score, SOFA score, ICU and hospital stay duration, and serum biomarkers were considered endpoints.

RESULTS: Ten HL-SAP patients accepted conventional treatment alone (the control group) and 10 patients underwent HVHF&HP combined with conventional treatment (the HVHF&HP group). The APACHE II score, SOFA score, systolic blood pressure, diastolic blood pressure, heart rate, serum amylase, and serum creatinine were significantly reduced after the HVHF&HP treatment. The changes in these variables were significantly different between the HVHF&HP and control group at 48 hours after the initiation of treatment. Patients in the HVHF&HP group had a significantly shorter ICU stay ($P=.015$). The reduction in serum triglyceride and cholesterol in the HVHF&HP group after 2, 6, 12, 24, and 48 hours was greater than the control group. All of the tested serum cytokines were significantly decreased after HVHF&HP treatment ($P<.05$). However, in patients who underwent conventional treatment alone, there was no significant change in the serum cytokines.

CONCLUSION: This study suggests that the addition of HVHF&HP to conventional treatment for HL-SAP patients may be superior to conventional treatment alone for the improvement of serum biomarkers and clinical outcomes.

Severe acute pancreatitis (SAP) is a life-threatening condition which may cause systematic inflammatory response syndrome (SIRS), sepsis, and even multiple organ dysfunction syndromes (MODS). Cholelithiasis, alcohol abuse, and hyperlipidemia are the main causes of acute pancreatitis. The morbidity of SAP secondary to hyperlipidemia (HL-SAP) has apparently increased in recent years. SAP occurred in 12-38% of hyperlipidemic patients.^{1,2}

The main treatment for HL-SAP is to decrease the serum triglyceride level and prevent a systemic inflam-

matory response.³ Although serum triglyceride can be decreased by plasmapheresis, it is not widely used in clinical practice because of the limited availability of plasma donors especially in developing countries.⁴⁻⁶ Continuous veno-venous hemofiltration (CVVH), especially high-volume hemofiltration (HVHF), has been widely used for treating SAP because it can effectively remove the excessive inflammatory mediators from the system circulation and help maintain homeostasis. However, CVVH does not allow large molecules such as triglycerides to pass through the hemofilter.

Hemoperfusion (HP) is another blood purification modality which can absorb large pathogenic molecules from the circulation by adsorbent materials installed in the HP cartridge. HP is more effective in removing middle and large molecules and toxins bonded with proteins than CVVH. In 2011, Tang et al successfully treated a pregnant woman with hyperlipidemic pancreatitis by using CVVH and HP.⁷ However, to the best of our knowledge, the evidence for using HVHF&HP for HL-SAP is limited to anecdotal descriptions. Therefore, we evaluated the efficacy of HVHF&HP combined with conventional treatment versus conventional treatment alone for HL-SAP in a prospective controlled study.

PATIENTS AND METHODS

This was a prospective controlled study conducted between May 2010 and May 2013. HL-SAP patients admitted to our intensive care unit (ICU) who underwent experimental HVHF&HP treatment based on conventional treatment and HL-SAP patients who underwent conventional treatment alone were prospectively followed. Exclusion criteria were the following: i) flare-up of chronic pancreatitis, ii) previous exploratory laparotomy during the current episode of pancreatitis, iii) pancreatitis caused by abdominal surgery, iv) CVVH treatment prior to admission, v) patients had other indications for CVVH, such as hyperkalemia, acute kidney failure, and so on. The protocol of the present study complied with the protocol and principles of the Declaration of Helsinki and was approved by the ethic committee of our hospital. Written informed consent was obtained from all patients or their legal guardians.

A diagnosis of HL-SAP was made according to the Atlanta criteria⁸ and the guidelines for the management of acute pancreatitis issued by the World Congress of Gastroenterology.⁹ SIRS and MODS were diagnosed using the criteria of the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM), respectively.¹⁰

All patients received standard conventional treatment, including aggressive fluid resuscitation, oxygen supplementation, gastrointestinal decompression, insulin and/or heparin treatment, oral antihyperlipidemic drug therapy, dietary interventions, nutritional support, prophylactic antibiotics, and drainage of peripancreatic abscesses.⁸⁻¹²

In addition to the standard conventional treatment, patients in the HVHF&HP group underwent two cycles of HVHF&HP treatment. Each cycle included 24 hours of HVHF and 2 hours of HP. The HVHF&HP treatment was initiated in the first 48 hours after the ICU admission. At first, a double lumen catheter was

inserted into the internal jugular to establish vascular access. Secondly, HVHF was performed with a Diapact CRRT machine (B. Braun, <http://www.bbraun.com/cps/rde/xchg/bbraun-com>). The blood flow rates ranged from 250 to 300 mL/min. The substitution fluid was infused at a rate of 70 mL/kg/h in a pre-diluted manner (before the hemofilter). An AN69 hemofilter (1.6 m² surface area, 35-KD limit; Baxter Healthcare Corp. Deerfield, IL, USA, <http://www.baxter.com/>) was used and changed every 24 hours or at the occurrence of filter dysfunction. The anticoagulant was low molecular weight heparin or no anticoagulant when there was any contraindication for anticoagulant treatment. Two hours of HP was carried out every 24 hours using a synthetic resin cartridge (HA-330; Zhuhai Lizhu Group, Biological Material Co, Ltd., China) installed before the hemofilter.

Body temperature, breathing rate, blood pressure, heart rate, central venous pressure, PaO₂ and FiO₂ were tested and recorded every 6 hours. Biochemical parameters including platelet count, serum creatinine, base excess, and blood calcium were tested and recorded every 24 hours. Acute Physiology and Chronic Health Evaluation II (APACHE II) scores and Sequential Organ Failure Assessment (SOFA) scores were calculated to evaluate the severity of the disease at 2-, 6-, 12-, 24-, and 48-hour after the treatment. Blood and effluent samples were taken before the initiation of treatment (0 h) and at 2-, 6-, 12-, 24-, and 48-hour. IL-1, IL-2, IL-6, IL-8, IL-10, and TNF- α concentrations were tested by using quantitative colormetric sandwich ELISA kits (Shanghai Senxiong Science and Technology Company, China). All measurements were performed according to the protocols provided by the manufacturers. Every sample was tested twice and the mean cytokine concentration was calculated and used in the analyses. The researcher who performed the tests was blinded to the patients' treatment and baseline data.

Statistical analysis

Continuous variables are expressed as the mean and standard deviation. The differences in continuous variables between the control and HVHF&HP groups were estimated by the Mann-Whitney U test. The Wilcoxon matched-pairs test was used to evaluate the internal group differences for continuous variables. For discontinuous variables, the chi-square and Fisher's exact tests were used to evaluate the differences between groups. All of the statistical analyses were performed using the statistical package SPSS (version 12.0; SPSS Inc., Chicago, IL, USA). *P* values <.05 were considered to be statistically significant.

RESULTS

The mean (SD) age were 40.3 (7.6) years and 43.2 (7.0) years for the patients in the HVHF&HP and the control group, respectively (Table 1). APACHE II scores were 13.33 (1.68) for the treatment group and 14.0 (0.4) for the control group. There were no significant differences in baseline characteristics between the two groups before treatment (Table 1).

Change in clinical features

Only one patient in the control group died during the ICU stay and the causes of death were ARDS and cardiogenic shock. The two groups were not significantly different in ICU mortality rate ($P=.99$). After 48 hours, the average APACHE II score of the HVHF&HP group decreased from 14.00 (0.37) to 5.44 (0.46)

($P<.05$). However, the reduction of the APACHE II score of the control group was not significant (0-hour: 13.33 [1.68], 48-hour: 12.00 [2.87], $P>.05$, Table 2). The two groups were significantly different in the change in APACHE II score at 6, 12, 24, and 48 hours after the start of the treatment (Table 2). The change in SOFA score after 48 hours treatment was significant for the HVHF&HP group (baseline: 10.00 [0.36], after 48 hours treatment: 4.07 [0.38], $P<.05$), but was not significant for the control group (0-hour: 10.67 [1.35], 48-hour: 8.98 [0.63], $P\geq.05$, Table 2). The differences in the change of SOFA score between groups were significant at 6, 12, 24, and 48 hours.

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were significantly improved in the patients who underwent HVHF&HP treatment, but were not significantly changed in the patients who underwent conventional treatment alone ($P<.05$, Table 2). Mean heart rates in the HVHF&HP group decreased from 134.38 (2.23) to 82.49 (0.71) ($P<.05$). Serum amylase and creatinine levels gradually decreased during HVHF&HP treatment. Changes in SBP, DBP, heart rate, serum amylase level, and serum creatinine level at 48 hours were significantly different between the two groups (Table 2).

Patients who underwent HVHF&HP plus conventional treatment had a significantly shorter ICU stay duration (10.1 [3.8] days versus 16.0 [5.0] days, $P=.015$) than patients underwent conventional treatment alone. The HVHF&HP group tended to have a shorter period of hospitalization (17.4 [3.9] days versus 22.6 [6.6] days, $P=.105$), compared with the control group.

All patients were followed for up to 6 months, and no recurrence of pancreatitis or death was observed during the 6 months follow-up. No adverse event was observed during HVHF&HP treatment. The means of the total medical cost were RMB 62000 and 50000 for the HVHF&HP and control groups, respectively.

Change in serum lipid level

The serum lipid levels were significantly reduced after 48 hours of HVHF&HP treatment. The mean serum triglyceride (TG) level was reduced to 10.62 (1.78) mmol/L at 2 hours ($P<.05$) and 2.92 (1.03) mmol/L at 48 hours ($P<.05$) in the HVHF&HP group. The mean serum cholesterol (CHO) level in the HVHF&HP group was reduced from 11.68 (1.37) mmol/L to 6.9 (1.02) mmol/L at 2 hours ($P<.05$) and 4.10 (1.00) mmol/L at 48 hours ($P<.05$). However, the mean serum TG (0 hour: 27.53 [1.68] mmol/L, 48 hours: 19.39 [2.01] mmol/L, $P\geq.05$) and CHO (0 hour: 11.20 [1.64] mmol/L, 48 hours: 10.10 [1.10] mmol/L,

Table 1. Baseline characteristics of the in the HVHF&HP group and the control group.

| Variables | Control (n=10) | HVHF&HP (n=10) | P value |
|--|------------------|------------------|---------|
| Male, n (%) | 8 (80%) | 7 (70%) | .99 |
| Age (years) | 40.25 (1.63) | 43.2 (1.03) | .30 |
| APACHE II | 13.33 (1.68) | 14.00 (0.37) | .23 |
| SOFA | 10.67 (1.35) | 10.00 (0.36) | .15 |
| ARDS, n (%) | 6 (60%) | 7 (70%) | .99 |
| Mechanical ventilation, n (%) | 7 (70%) | 7 (70%) | .99 |
| Vasopressor, n (%) | 8 (80%) | 9 (90%) | .99 |
| DIC, n (%) | 1 (10%) | 1 (10%) | .99 |
| Serum creatinine ($\mu\text{mol/L}$) | 209.67 (67.79) | 205.8 (19.56) | .86 |
| BUN (mmol/L) | 11.93 (2.51) | 11.66 (0.80) | .75 |
| PH | 7.12 (0.16) | 7.10 (0.01) | .70 |
| HCO ₃ (mmol/L) | 12.00 (0.94) | 14.10 (0.89) | .22 |
| BE (mmol/L) | -9.87 (0.44) | -10.82 (0.84) | .21 |
| WBC (10 ⁹ /L) | 19.95 (0.29) | 22.74 (0.35) | .34 |
| Hemoglobin (g/L) | 140.50 (11.55) | 143.67 (3.05) | .41 |
| Albumin (g/L) | 34.60 (2.36) | 31.97 (0.76) | .21 |
| Serum amylase (IU/L) | 1284.50 (143.54) | 1455.30 (135.00) | .43 |
| SBP (mm Hg) | 149.00 (0.47) | 153.57 (2.30) | .33 |
| DBP (mm Hg) | 79.50 (3.06) | 82.33 (1.00) | .51 |
| Heart rate (bpm) | 134.00 (5.46) | 134.38 (2.23) | .84 |

ARDS, Acute respiratory distress syndrome ; APACHE II, Acute Physiology and Chronic Health Evaluation II score; BE, base excess; BUN, blood urea nitrogen; DBP, diastolic blood pressure; DIC, Disseminated intravascular coagulation; SBP, systolic blood pressure; SOFA, Sequential Organ Failure Assessment score; WBC, white blood cell.

Table 2. Changes in clinical laboratory variables in the HVHF&HP group vs the control group.

| Time points | APACHE II | | SOFA | | SBP (mm Hg) | | DBP (mm Hg) | | Heart rate (bpm) | | Serum amylase (IU/L) | | Serum creatinine (μmol/L) | |
|-------------|--------------|----------------------------|--------------|---------------------------|---------------|-----------------------------|---------------------------|----------------------------|------------------|-----------------------------|-----------------------------|-------------------------------|---------------------------|-----------------------------|
| | Control | HVHF & HP | Control | HVHF & HP | Control | HVHF & HP | Control | HVHF & HP | Control | HVHF & HP | Control | HVHF & HP | Control | HVHF & HP |
| 0 hr | 13.33 (1.68) | 14.00 (0.37) | 10.67 (1.35) | 10.00 (0.36) | 149.00 (0.47) | 153.57 (2.30) | 79.50 (3.06) | 82.33 (1.00) | 134.00 (5.46) | 134.38 (2.23) | 1284.50 (143.54) | 1455.30 (135.00) | 209.67 (67.79) | 205.8 (19.56) |
| 2 hrs | 12.93 (1.28) | 13.08 (0.46) | 10.17 (1.31) | 6.71 (0.38) | 149.95 (0.62) | 134.76 (2.68) ^{ab} | 81.50 (2.64) | 80.03 (1.07) | 133.00 (5.64) | 134.31 (2.74) | 901.90 (115.29) | 555.30 (121.00) ^{ab} | 208.91 (79.32) | 190.18 (16.67) ^b |
| 6 hrs | 12.00 (1.76) | 10.25 (0.32) ^{ab} | 10.00 (0.94) | 4.88 (0.28) ^{ab} | 145.75 (3.17) | 134.43 (1.60) ^{ab} | 86.00 (1.53) ^b | 77.00 (0.67) ^b | 131.00 (1.17) | 122.00 (1.24) ^{ab} | 830.75 (83.44) | 484.38 (78.30) ^{ab} | 207.0 (62.0) | 174.8 (15.25) ^{ab} |
| 12 hrs | 12.00 (1.76) | 9.00 (0.33) ^{ab} | 10.50 (0.71) | 3.88 (0.17) ^{ab} | 147.00 (5.82) | 135.00 (2.17) ^{ab} | 83.00 (3.95) | 76.33 (0.47) ^{ab} | 131.75 (5.10) | 131.75 (5.10) | 853.75 (70.29) | 359.88 (34.40) ^{ab} | 208.0 (46.53) | 169.7 (15.14) ^{ab} |
| 24 hrs | 12.00 (1.76) | 6.33 (0.36) ^{ab} | 9.67 (0.51) | 4.00 (0.27) ^{ab} | 148.33 (2.83) | 129.00 (1.20) ^{ab} | 80.33 (1.18) | 76.291 (0.92) ^a | 129.25 (7.07) | 94.38 (0.82) ^{ab} | 813.25 (55.33) ^a | 260.78 (27.79) ^{ab} | 211.0 (52.54) | 146.5 (14.34) ^{ab} |
| 48 hrs | 12.00 (2.87) | 5.44 (0.46) ^{ab} | 8.98 (0.63) | 4.07 (0.38) ^{ab} | 149.47 (3.72) | 127.11 (2.32) ^{ab} | 82.45 (2.42) | 70.21 (0.28) ^{ab} | 125.45 (7.18) | 82.49 (0.71) ^{ab} | 924.52 (57.67) | 213.87 (29.99) ^{ab} | 209.90 (11.24) | 125.5 (12.42) ^{ab} |

APACHE II, Acute Physiology and Chronic Health Evaluation II score; DBP, diastolic blood pressure; SOFA, Sequential Organ Failure Assessment score; Hr, hour; SBP, systolic blood pressure. ^a Identifies these variables differ significantly from their baseline value; ^b Identifies these variables differ significantly from the control group.

$P \geq .05$) levels in the control group were not significantly reduced after 48 hours of conventional treatment alone (Figure 1). The changes in the TG and CHO levels were significantly different between groups at 2, 6, 12, 24, and 48 hours (Figure 1).

Change of cytokines

After 2 hours of HVHF&HP treatment, the serum concentrations of all of the tested cytokines (including IL-1, IL-2, IL-6, IL-8, IL-10, and TNF- α) were significantly decreased (Figure 2). The serum concentrations of all of the tested cytokines were decreased to nearly normal after 48 hours of HVHF&HP treatment (Figure 2). We also found out that the serum levels of IL-1, IL-2, IL-6, IL-8, IL-10, and TNF- α in the effluent displacement liquid were increased gradually after 6, 12, and 24 hours of HVHF treatment (Figure 3). However, in the control group, serum IL-1, IL-2, IL-6, IL-8, IL-10, and TNF- α levels were not significantly decreased after 48 hours of conventional treatment alone, with a mean baseline value of 0.35 (0.02) ng/mL, 10.59 (0.72) ng/mL, 0.40 (0.04) ng/mL, 0.78 (0.03) ng/mL, 150.70 (13.63) ng/mL, and 78.11 (8.99) fmol/mL, respectively, and a mean 48-hour value of 0.310 (0.02) ng/mL, 10.94 (0.83) ng/mL, 0.47 (0.02) ng/mL, 0.68 (0.06) ng/mL, 140.87 (12.21) ng/mL, and 91.80 (6.21) fmol/mL ($P > .05$, Figure 2), respectively. The changes in all of the cytokines after 48 hours of treatment were significantly different in the two groups ($P < .05$, Figure 2).

DISCUSSION

The incidence of AP caused by hyperlipidemia has shown a rising trend in the past decade. In 1995, Fortson et al reported on 577 AP patients from four centers and showed that the incidence of hyperlipidemic AP during 1982 and 1994 was 1.3%~3.8%.¹³ In 2003, the incidence of HL-SAP was reported to be 12%~38% and 12.3% by Mao et al¹⁴ and Chang et al,¹⁵ respectively.

The pathogenesis of hyperlipidemia-induced pancreatitis is not well understood. Previous studies have elucidated the following possible mechanisms. First, free fatty acids (FFAs), one of the products of triglyceride metabolism, cause direct damage to pancreatic acinar cells. Second, an increase in circulating FFA induces acidosis, which accelerates the activation of trypsinogen. Third, hyperlipidemia increases blood viscosity and FFAs damages the capillary endothelium, both of which lead to microcirculatory disturbances in the pancreas. Moreover, triglycerides play an important role in the occurrence and development of AP, which can

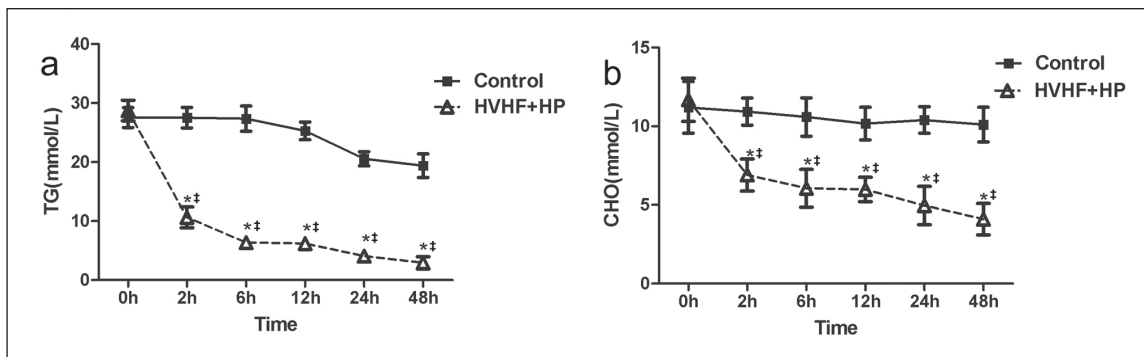


Figure 1. Serum CHO and TG levels at 0-, 2-, 6-, 12-, 24-, 48-hour after the initiation of treatment. *Variables differed significantly from their baseline value; †Variables differed significantly from the control group.

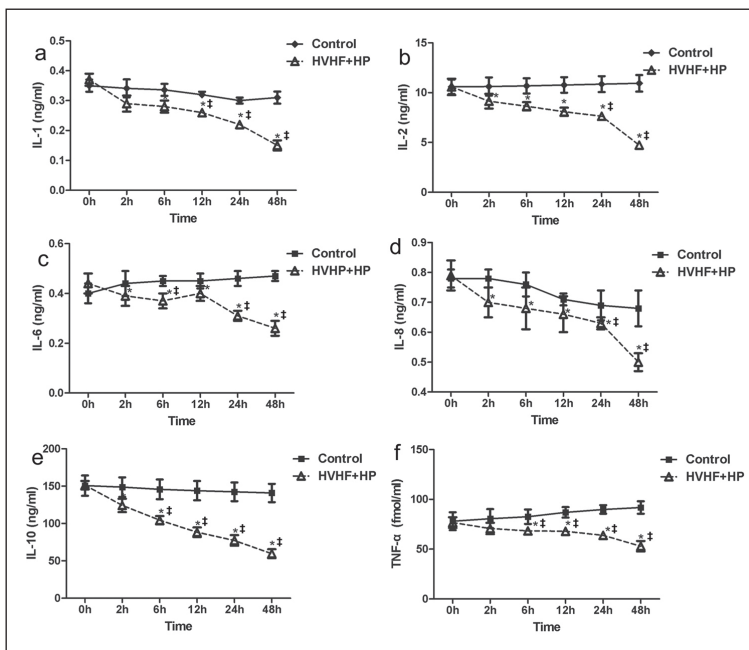


Figure 2. Serum IL-1, IL-2, IL-6, IL-8, IL-10, and TNF- α level at 0-, 2-, 6-, 12-, 24-, 48-hour after the initiation of treatment. *Variables differed significantly from their baseline value; †Variables differed significantly from the control group.

further aggravate pancreatic necrosis and cause severe pancreatitis.^{14,16} Serum triglyceride levels of 11.3-22.6 mmol/L have been associated with incidences of pancreatitis as high as 21%.^{2,16} Early and rapid reduction of serum triglyceride to <5.65 mmol/L could prevent further development of pancreatitis.^{17, 18}

How can we effectively and rapidly reduce triglycerides and thereby prevent the resultant damage to the pancreas? Several studies have proven that plasma replacement can swiftly reduce triglyceride and alleviate AP symptoms.^{15,19,20} Therefore, plasma replacement has become an effective alternate for pancreatitis. However,

plasma replacement is expensive and the use of plasma replacement is limited by many factors, including hospital plasma supply and plasma allocation time. Therefore, it is used sparingly in clinical practice. HP is an important hemopurification technique, and the adsorbent materials installed in the HP cartridge can effectively clear the hydrophobic substances that commonly bond to the serum proteins and lipids. Direct lipoprotein adsorption without initial plasma separation is the primary HP technique for extracorporeal CHO and TG elimination, and can improve the patient symptoms impressively. Tasaki et al and Bosch et al showed that direct HP was an effective and safe method for the clearance of serum lipoprotein (a) (Lp[a]) and triglyceride.^{21,22} In 2011, Tang et al successfully managed a pregnant woman with hyperlipidemic pancreatitis by the early use of CVVH and HP.⁷ In our present study, HVHF&HP was successfully used in 10 HL-SAP patients. The results indicate that blood lipids level (TG and CHO) significantly decreased after every HP session, and the serum amylase concentration significantly decreased after the second HP session. Rapid elimination of the blood lipids was associated with dramatic alleviation of patient symptoms and reduction of the APACHE II and SOFA score.

Based on the pathogenesis of SAP, the pancreatic autophagy theory appears to be insufficient to fully explain the occurrence and development of SAP. In 1988, Rinderknecht et al proposed the theory of “excessive activation of leukocyte”.²³ Recently, the “second strike theory”, i.e., the productions of inflammatory cytokines, and the “cascade reaction”, are considered as the primary causes for progression of pancreatitis to multiple-organ failure and death. Continuous HE, especially HVHF, has proved to be effective in the clearance of inflammatory mediators, reconstitution of the immune system, stabilization of the internal environment, preservation

of organ function, and a reduction in mortality rate.²⁴⁻²⁶ However, HVHF is not effective in the clearance of large molecules. Mao et al found that coupled plasma filtration adsorption (CPFA) was better than HVHF in increasing the anti-inflammatory to pro-inflammatory mediator ratios, improving the antigen presentation ability, and restoring leukocyte responsiveness.²⁷ Accordingly, we hypothesized that the combination of HVHF with HP would eliminate blood lipids and serum inflammatory cytokines and preserve the homeostasis and fluid-electrolyte balance. Two cycles of HVHF&HP treatment were performed for the patients in the HVHF&HP group. Significant reductions of TG, CHO, IL-1, IL-2, IL-6, IL-8, IL-10, and TNF- α were observed after the treatment, compared with either the baseline values or the control group. The reductions in these serum biomarkers were consistent with the improvement of patient physical status. IL-1, IL-2, IL-6, IL-8, IL-10, and TNF- α were reported to be the main inducers of hepatic synthesis of acute-phase protein response. The level of these cytokines was reported to directly relate to the degree of various types of organ damage in AP patients. Therefore, most likely, both the clearance of blood lipids by HP and the clearance of serum inflammatory cytokines by HVHF contributed to the improvement of the APACHE II and SOFA score and the reduction of ICU duration of stay in the HVHF&HP group.

LIMITATIONS

The present study was performed in a single center with a small sample size. The application of the conclusions to other centers should be with caution. Additionally, the present study was not designed to evaluate the mortality difference between the two groups. The efficacy of the combination of HVHF&HP with conventional treatment on patient survival has not been well assessed. Therefore, we are designing an RCT with large sample size to evaluate the efficacy of HVHF&HP on

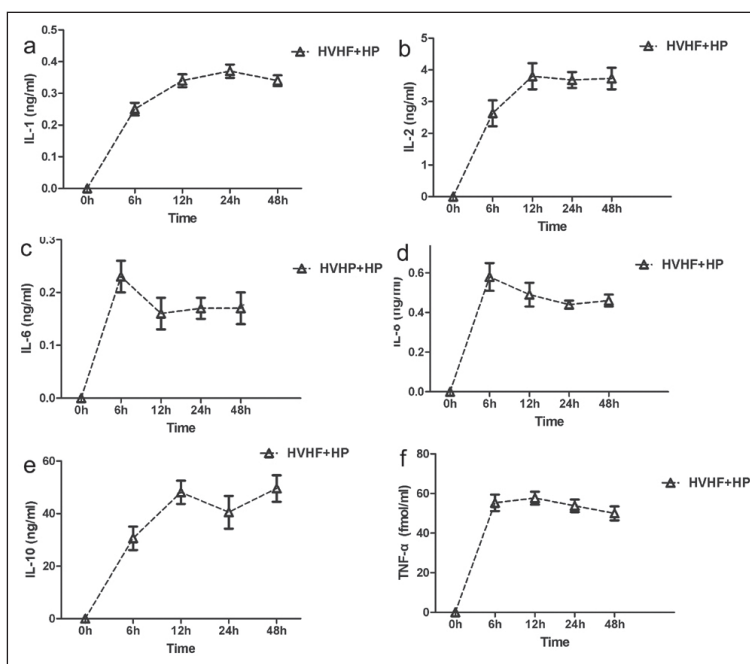


Figure 2. Serum IL-1, IL-2, IL-6, IL-8, IL-10, and TNF- α level at 0-, 2-, 6-, 12-, 24-, 48-hour after the initiation of treatment. *Variables differed significantly from their baseline value; †Variables differed significantly from the control group.

long-term survival of HL-ASP patients. Further trials on this subject from other centers are needed as well.

CONCLUSION

In conclusion, the combination of HVHF&HP with conventional treatment for HL-SAP patients could effectively decrease the level of serum cytokines and improve patient physical status. Further studies are needed to evaluate the efficacy of HVHF&HP on patient mortality.

Conflict of interest

No conflict of interest is declared.

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