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Evaluation of HVHF for the treatment of severe acute pancreatitis accompanying MODS

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Abstract

Systemic inflammatory response syndrome (SIRS) prevention is key to severe acute pancreatitis (SAP) treatment and the assessment of high-volume hemofiltration (HVHF) for treating SAP accompanying multiple organ dysfunction syndromes.

In this prospective controlled study, 40 SAP patients were divided into 2 groups: control (n = 22, treated with fasting, decompression, and intravenous somatostatin) and HVHF (n = 18, HVHF administration in addition to the treatment in the control group) groups; and were assessed for serum and urine amylase, WBC, C-reactive protein (CRP), and hepatic and renal functions. Vital signs and abdominal symptoms were recorded, and complications and mortality were analyzed.

APACHE II scores in the HVHF group were significantly lower than in the control group at 3 and 7 days (6.3 ± 1.7 vs 9.2 ± 2.1 and 3.3 ± 0.8 vs 6.2 ± 1.7, respectively). Compared with controls, serum, and urine amylase, WBC, CRP, and organ functions significantly improved after HVHF treatment. Meanwhile, mortality (16.7% vs 31.8%) and complication (11.1% vs 40.9%) rates were significantly reduced.

The other clinical parameters were significantly ameliorated by HVHF. HVHF rapidly reduces abdominal symptoms and improves prognosis, reducing mortality in SAP patients; and is likely through systemic inflammatory response syndrome attenuation in the early disease stage.

Abbreviations: APA = American Pancreatic Association, CRP = C-reactive protein, HVHF = high-volume hemofiltration, IPA = International Association of Pancreatology, L-1β = interleukin-1β, MODS = multiple organ dysfunction syndrome, SAP = severe acute pancreatitis, SD = standard deviation, SIRS = systemic inflammatory response syndrome, TNF-α = tumor necrosis factor-α.

Keywords: high-volume hemofiltration, multiorgan dysfunction, severe acute pancreatitis, systemic inflammatory response syndrome

1. Introduction

Severe acute pancreatitis (SAP) is one of the most common acute severe diseases in clinical practice.[1] At the early stage, an enormous release of inflammatory cytokines and toxins in the blood results in systemic inflammatory response syndrome (SIRS), which is the major cause of multiple organ dysfunction syndrome (MODS).

According to the studies, SAP is a devastating disease that is associated with mortality ranging from less than 10% to as high as 85%.[2–9] The main causes of this disease include gallbladder and biliary stone,[10] hypertriglyceridemia, alcohol,[11] pancreatic structure,[12] and secondary AP.[13,14]

Therefore, efficacious clinical therapies to prevent disease progression and improve prognosis are urgently needed.

In recent years, with the increasing understanding of SAP disease mechanism, multiple studies have considered SAP as a severe SIRS resulting from pancreatic autodigestion; that is, inflammatory cells are activated to release significant amounts of cytokines, and its downstream reactions are critical to SAP progression.[15,16] SAP-induced ischemia, injury, necrosis and endotoxemia lead to increased levels of tumor necrosis factor-α (TNF-α) and interleukin-1β (L-1β) in the circulation; and further induce IL-6 and IL-8 production. This sequentially results in hypercytokinemia, SIRS, shock, loss of inner homeostasis, and organ dysfunction. Therefore, preventing and blocking SIRS initiation and progression is a key in the treatment of SAP, and plays a critical role in the prevention and control of MODS initiation and development.[17] At present, the therapeutic strategy for SAP has switched the priority from surgery to comprehensive treatment with nonsurgical methods, with use of short-term high-volume veno-venous hemofiltration, which has a beneficial impact on the management of SAP.[18] High-volume hemofiltration (HVHF) can selectively eliminate serum molecules smaller than the pore size of the filter membrane used. Indeed, important amount of cytokines released during SAP can be filtered out by HVHF. In using HVHF to treat pig models of septic shock, it was found that hemofiltration at 6 L/h improved arterial pressure, cardiac output, and left and right ventricular diastolic function. Some recent clinical reports have shown that HVHF relieves SAP symptoms, shortens the disease course, lowers mortality, and reduces hospitalization time.[19]

2. Materials and methods

2.1. Patients

Patients were recruited from December 2011 to December 2013 in this perspective, nonrandomized controlled trial, which was

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carried out in the First Affiliated Hospital of Xinjiang Medical University, Urimqi, China. The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University, and informed consent was signed by patients and their families before the examination and treatment.

Inclusion criteria were as follows: SAP patients who were 25 to 77 years of age, duration from disease onset to hospitalization was within 48 hours, and disease progression to MODS with an APACHE II ranking of 7–34 and Balthazar CT staging between D and E. Exclusion criteria were as follows: acute renal failure before disease onset, pregnant women, and subjects with malignant tumors or immune defects. Patients with chronic kidney disease requiring regular hemofiltration or those with known biliary obstruction were also excluded.

2.2. Diagnostic criteria

SAP diagnosis in all patients was in line with the SAP diagnostic standards in the Draft criteria for diagnosis and treatment of acute pancreatitis in China (2014), which was established by The Academic Group of Pancreatic Disease, Branch Association of Digestive Disease, Chinese Medical Academic Association,[20] and Atlanta classification of Acute Pancreatitis.[21]

During hospitalization, MODS was evaluated based on the widely recognized Multiple Organ Dysfunction Score by Marshall et al.[22] In brief, the functions of 5 major organs (lung, liver, kidney, hemodynamics, and awareness) were evaluated on a daily basis. Scores ranged from 0 (no dysfunction) to 4 (severe dysfunction). Scores 3 and 4 were considered to reflect organ dysfunction.

The diagnostic standards of biliary pancreatitis established by Fölsch et al. were as follows: abdominal beta ultrasound and CT scan calculus were found; 2 of the statements (1) ALP ≥125 U/L, (2) ALT ≥75 U/L, and (3) TBIL ≥2.3 mg/dL were verified.[23]

2.3. Grouping

According to the parity of the hospitalization number, patients were prospectively divided into 2 groups. The control group comprised of 22 patients. Among these patients, 11 were male and 11 were female; and the average age of these patients was 50.55 ± 14.99 years. The HVHF group comprised of 18 patients. Among these patients, 14 were males and 4 were females; and the average age of these patients was 53.94 ± 16.46 years.

2.4. Treatment

The patients in the control group underwent fasting, decompression, and continuous intravenous perfusion of somatostatin during their hospitalization. Somatostatin (Stilamin, Serono Co., Ltd. Switzerland; 3000 μg in 48 mL of 5% glucose) was infused intravenously using a micropump at 4 mL/h, qd.[20] For gastric acid neutralization, lansoprazole (Ao Wei Jia, Jiangsu Aosaikang Pharmaceutical Co., Ltd, China; 30 mg) + 0.9% sodium chloride (100 mL) were intravenously infused, bid. For effective blood volume supplementation, lactated Ringer's solution was chosen with priority. Recovery standards were referred to the International Association of Pancreatology (IPA)/American Pancreatic Association (APA) evidence-based guidelines for the management of acute pancreatitis (2013).[24] Patients orally took food together with nasogastric and enteral feeding for nutrition support. Supplementary nutrition indices were according to the IPA/APA evidence-based guidelines for the management of acute pancreatitis (2013).[24] The nutrition supply was evaluated and provided by specialized nutritionists of the Nutrition Department of our hospital. These comprised of the following: fat emulsion, amino acids, and glucose injection (1440 mL) + vitamin C injection (2 g) + vitamin B6 injection (0.2 g) + 10% potassium chloride injection (40 mL) + 10% calcium gluconate injection (40 mL) + 10% sodium chloride injection (40 mL) + N(2)-L-alanyl-L-glutamine injection (10 g) + 2 fat-soluble vitamin II. Enteral nutrition emulsions (TPF-D, 500 mL) were fed through nasogastric and enteral tubing, bid. Antibiotic use was according to the IPA/APA evidence-based guidelines for the management of acute pancreatitis (2013)[24] and the Draft criteria for the diagnosis and treatment of acute pancreatitis in China (2014), established by The Academic Group of Pancreatic Disease, Branch Association of Digestive Disease, Chinese Medical Academic Association.[20] Antibiotic use was decided after consultation with clinical pharmacists in our hospital. The antibiotics used included latamoxef sodium (Hainan Hailing Pharmaceutical Co. Ltd, China, 1.5 g, intravenous infusion, bid), imipenem (Merck and Dohme Corp.; 1 g, intravenous infusion, q8h), and cefotiam hydrochloride (Harbin Pharmaceutical Group; 2 g, q12h). For the abdominal mirabilite pack, 500 g of mirabilite (Sichuan Chuanmei Mirabilite Co., Ltd., China) was packed in a special bag and placed on the surface of the projection of the pancreas. The pack was changed every 8 to 12 hours.[20]

Patients in the HVHF group received bedside HVHF treatment in addition to the treatment described for the control group. HVHF therapy was performed using an IQ hemofiltration machine (Japan). A double-lumen indwelling catheter was placed in the right femoral or subclavian vein to establish cardiopulmonary bypass. The high-volume continuous veno-venous hemofiltration mode was selected, with a blood flow rate set to 200 to 300 mL/min. The filter and tubules were preperfused with heparin saline (4000 U/L) for 20 minutes before hemofiltration using the set program. Replacement fluid was pumped in at 3.0 to 4.0 L/h using the postdilution mode. The electrolyte content and sodium bicarbonate amount used in the replacement fluid were adjusted according to blood gas analysis data and blood biochemistry tests. The hemofiltration volume was determined through the load capacity of the patients, which varied between 2000 and 3500 mL, daily. The hemofiltration lasted for ≥6 h/d, and the treatment between 4 and 9 days, with an average of 7 days. HVHF was terminated when the heart rate dropped below 100/min, respiration rate dropped below 25/min, abdominal symptoms or signs disappeared, or when organ intubation was removed, or renal function restored.

2.5. Outcomes

Patient body temperature, heart rate, respiration rate, blood pressure, and SaO_2 were monitored daily. Body temperature of <37°C, respiration rate of <25/min, heart rate of <100/min, and SaO_2 at >90% were considered normal. Routine blood test, blood and urine amylase, electrolyte levels, hepatic and renal functions, and C-reactive protein (CRP) amounts were examined before HVHF, and at days 3 and 7 during treatment. Abdominal signs in patients were carefully monitored daily. For patients with severe SAP, especially in case of disease worsening, intra-abdominal pressure should be considered. Intra-abdominal hypertension refers to the persistent or recurrent elevation of intra-abdominal pressure to >12 mm Hg. This was measured by intravesical perfusion with saline. In case of nonimprovement or worsening of clinical manifestations of SAP, beta-ultrasound, CT

and MR examinations should be repeated when invasive operation is planned. Changes in patient's vital signs were recorded to monitor the progression process of disease, and the occurrence of complications and death. Surgery and mortality rates, length of hospitalization, and procedure cost were evaluated.

2.6. Follow-ups

When patients were discharged, they were given heath related education and informed about the follow-ups, which were performed by phone, outpatient visit, and inpatient re-examination. Patient follow-up included 3 aspects: the prevention of recurrence, and the evaluation and treatment of local and general complications. Phone follow-ups were conducted by the authors once every other week for the first 3 months from discharge, and monthly thereafter. Outpatient visits were performed once every 3 months. Patients were followed-up for 2 years.

2.7. Statistics

Data were presented as mean ± standard deviation (SD), and were analyzed using SPSS 17.0 software (SPSS, Chicago, IL). Differences between both groups were assessed by *t*-test. Count data were evaluated by X^2-test. $P < .05$ was considered statistically significant.

3. Results

3.1. Patient baseline characteristics

There were no significant differences between both groups in terms of age, gender, ethnicity, CT staging, and etiology parameters such as gall stone and alcohol rates, WBC, serum and urine amylase levels, and CRP, BUN, Cr, ALT, and AST amounts (all $P > .05$, Table 1).

Table 1

Comparison of baseline information between the 2 groups.

	HVHF	Control	
	n = 18	n = 22	*P* value
Age, years	53.94 ± 16.46	50.55 ± 14.99	.49
Gender male, n%	14, 77.8%	11, 50.0%	.07
Ethnic			
Han, %	14, 77.8%	13, 59.1%	.23
Uyghur, %	3, 16.7%	5, 22.7%	.78
Others, %	1, 5.6%	4, 18.2%	.08
CT staging			
D, %	7, 38.9%	15, 68.2%	.23
E, %	5, 27.8%	1, 4.5%	.10
Others, %	6, 33.3%	6, 27.3%	.53
Etiology			
Gall stone, %	10, 55.6%	10, 45.5%	.12
Alcohol, %	1, 5.6%	0, 0.0%	.47
Others, %	7, 38.9%	12, 54.6%	.29
WBC	14.85 ± 4.68	14.29 ± 9.44	.87
Serum amylase	876.3 ± 178.0	619.9 ± 566.2	.12
Urine amylase	5391.1 ± 4235.2	4621.6 ± 728.8	.16
C-reactive protein	209.3 ± 171.4	227.8 ± 89.8	.85
BUN, mmol/L	13.1 ± 3.2	12.5 ± 2.7	.26
Cr, μmol/L	267 ± 48	263 ± 52	.83
ALT	245.46 ± 157.36	270.32 ± 67.00	.67
AST	241.79 ± 195.07	296.82 ± 29.92	.47

3.2. HVHF treatment results in improved clinical outcomes

HVHF treatment significantly reduced abdominal pain (49 ± 15 hours vs 74 ± 36 hours, $P < .05$) and abdominal tenderness (67 ± 19 hours vs 105 ± 37 hours, $P < .05$) relief times in patients, compared with the control group, as summarized in Table 2. A similar trend was obtained for intubation times (123 ± 34 hours vs 165 ± 43 hours, $P < .05$), complication rates (11.1% vs 40.9%), surgery rates (16.7% vs 86.4%), death incidences (16.7% vs 31.8%), and average hospital stay (17.45 ± 6.32 days vs 25.32 ± 7.67 days), with all values markedly reduced in HVHF, compared with controls (all $P < .05$). However, average hospitalization costs were similar between both groups ($P > .05$, Table 2).

3.3. HVHF treatment results in improved clinical and grading indices

Before treatment, APACHE II scores in the 2 groups were not significantly different. On day 3 of treatment, APACHE II scores of HVHF-treated patients were significantly lower than controls (6.3 ± 1.7 vs 9.2 ± 2.1, $P < .05$). Although APACHE II scores decreased with time in both groups, the values obtained for HVHF-treated patients were still significantly lower than those of controls (3.3 ± 0.8 vs 6.2 ± 1.7, $P < .05$; Table 3).

Normal body temperature, respiration, heart and SaO_2 rates between both the groups were similar before treatment. However, these values were all significantly higher in the HVHF group than in the control group at days three and 7 ($P < .05$), with sharper differences obtained at day 3 compared to day 7 (Table 3).

3.4. Dynamic changes of serum and urine amylase levels after treatment

HVHF-treated patients and controls had similar serum amylase levels before treatment ($P > .05$). On day 3, serum amylase levels of 243.1 ± 42.0 and 477.8 ± 117.7 U/L were obtained for patients in the HVHF and control groups, respectively; indicating a significant decrease after HVHF treatment ($P < .05$). These values dropped in both groups at day 7 of treatment. However, HVHF-treated patients revealed even lower serum amylase levels compared with controls (169.5 ± 84.3 vs 311.5 ± 13.4 U/L, $P < .05$). Similarly, no significant differences were noted in urine amylase levels between HVHF-treated patients and controls ($P > .05$) before treatment. On day 3 of treatment, urine amylase levels in the HVHF group were reduced compared with the control group; but the difference was not statistically significant ($P > .05$). These values also decreased with time, but a more

Table 2

Comparison of clinical outcomes between the 2 groups.

	HVHF	Control	*P* value
Abdominal pain relief time, h	49 ± 15	74 ± 36	.02
Abdominal tenderness relief time, h	67 ± 19	105 ± 37	.04
Intubation time, h	123 ± 34	165 ± 43	.04
Complication rate (n, %)	2, 11.1%	9, 40.9%	.02
Surgery rate (n, %)	3, 16.7%	19, 86.4%	.03
Death rate (n, %)	3, 16.7%	7, 31.8%	.04
Average hospitalization time, day	17.45 ± 6.32	25.32 ± 7.67	.04
Hospitalization cost (10k RMB)	17.69 ± 12.40	15.57 ± 7.03	.74

Table 3

Comparison of clinical data on day 3 and day 7 between the 2 groups.

	Day 3			Day 7		
	HVHF	Control	*P*	HVHF	Control	*P*
Body temperature normal rate, %	11, 61.1%	3, 13.6%	.02	17, 94.4%	14, 63.6%	.04
Heart rate normal rate, %	12, 66.7%	4, 18.2%	.02	17, 94.4%	14, 63.6%	.04
Respiration normal rate, %	12, 66.7%	4, 18.2%	.02	17, 94.4%	14, 63.6%	.04
SaO_2 Normal rate, %	13, 72.2%	5, 22.7%	.01	17, 94.4%	14, 63.6%	.04
APACHE II score	6.3±1.7	9.2±2.1	.04	3.3±0.8	6.2±1.7	.03
WBC	9.57±5.53	10.97±5.03	.28	7.71±3.47	10.12±5.07	.04
Serum amylase	243.1±42.0	477.8±117.7	.04	169.5±84.3	311.5±13.4	.03
urine amylase	1173.5±558.2	1637.2±836.7	.14	440.4±390.4	840.3±227.0	.04
C-reactive protein	157.9±35.6	172.3±38.5	.12	41.3±22.1	183.6±42.5	.02
BUN, mmol/L	7.1±1.9	11.6±2.3	.03	4.9±0.7	8.7±1.4	.01
Cr, μmol/L	93±23	201±43	.02	79±21	175±47	.01
ALT	109.27±89.76	131.00±21.07	.09	51.69±41.32	125.55±22.89	.03
AST	102.79±88.38	137.50±28.65	.28	69.75±58.76	129.18±19.33	.04

HVHF = high-volume hemofiltration

pronounced decrease occurred after treatment with HVHF, which resulted in a statistically significant difference between both groups (440.4±390.4 vs 840.3±227.0 U/L) at day 7 (Table 3).

3.5. Dynamic changes in white blood cells and CRP after treatment

There were no significant differences in white blood cell and CRP amounts between both groups before treatment ($P > .05$). On day 3 of treatment, HVHF-treated patients revealed less white blood cells ($9.57 \pm 5.53 \times 10^9$/L vs $10.97 \pm 5.03 \times 10^9$/L) and decreased CRP levels (157.9±35.6 mg/L vs 172.3±38.5 mg/L), than controls; but the differences were not statistically significant ($P > .05$). However, these values dropped considerably in HVHF-treated patients, unlike the values in controls. Indeed, compared with the control group, the HVHF group revealed significantly lower WBC amounts ($7.71 \pm 3.47 \times 10^9$/L vs $10.12 \pm 5.07 \times 10^9$/L) and CRP levels (41.3±22.1 mg/L vs 183.6±42.5 mg/L) at day 7.

3.6. Dynamic changes of renal function after treatment

There were no differences in renal function indicators such as BUN and Cr levels between controls and HVHF-treated patients before treatment. On days 3 and 7 of the treatment period, HVHF-treated patients revealed significantly lower BUN (day 3, 7.1±1.9 mM vs 11.6±2.3 mM; day 7, 4.9±0.7 mM vs 8.7±1.4 mM; all $P < .05$) and Cr (day 3, 93±23 mM vs 201±43 mM; day 7, 79±21 mM vs 175±47 mM; all $P < .05$) than controls (Table 3).

3.7. Dynamic changes of hepatic function after treatment

There were no significant differences in ALT and AST levels between both groups before treatment ($P > .05$). On day 3 of treatment, HVHF-treated patients revealed reduced ALT (109.27±89.76 U/L vs 131.00±21.07 U/L) and AST (102.79±88.38 U/L vs 137.50±28.65 U/L) levels compared with controls, but the differences were not statistically significant ($P > .05$). However, these values markedly declined at day 7 in the HVHF group, unlike the values in control group. This resulted in significant differences between both groups in ALT (51.69±41.32 U/L vs 125.55±22.89 U/L) and AST (69.75±58.76 U/L vs 129.18±19.33 U/L) levels.

4. Discussion

Several parameters were used to compare controls with patients that received treatment supplemented with HVHF: APACHE II scores, serum, and urine amylase levels, WBC and CRP amounts, and hepatic and renal functions, mortality and complication rates, abdominal pain relief duration, abdominal tenderness relief duration, and hospitalization length. We found that these indices all significantly improved in the HVHF group. Meanwhile, no significant difference was found in treatment costs between both the groups.

After HVHF, respiration, heart rate, and SaO_2 worsening were controlled. Among the 18 HVHF-treated patients, >11 patients recovered to normal levels in terms of body temperature, heart, respiration, and SaO_2 rates at day 3 of treatment. At day 7, almost all patients revealed normal values for these parameters in the HVHF group. It is noteworthy to mention that these values were significantly higher compared with the values obtained for patients in the control group at both time points.

In addition, mortality and complication rates were very low in the HVHF group, while 2 to 3 patients' complications or death in the control group. It was recently demonstrated that both somatostatin and octreotide appear to significantly reduce the mortality rate without any effect on the incidence of complications in SAP patients.[25] In a large study that compared conservative treatment (with somatostatin) and surgical intervention, a cure rate of 82.29% and a mortality rate of 13.54% were obtained in the conservative group, with no statistically significant difference between both treatment groups.[26]

APACHE II scores are widely used for risk stratification of patients newly admitted to ICU. While APACHE II has the problem of being less useful beyond 24 hours of admission, it is still closely related to the severity of SAP. It has been reported that APACHE II scores may be evaluated daily to monitor the disease course and the response to therapy.[27] In another study, researchers also pointed out that because SAP is a disease process in evolution, deteriorating APACHE II scores can identify patients who are highly likely to develop complications or a fatal

outcome.[28] Moreover, Khanna et al[29] suggested that APACHE II score was a specific and accurate method to predict organ failure and mortality, with an accuracy of 83.3% for organ failure, and 100% sensitivity and NPV for mortality. Therefore, we included APACHE II scores in the current study as an index to evaluate and compare outcomes of the patients in different groups. In addition, HVHF alleviates local inflammatory response in lungs, reduces the permeability of epithelial cells in lung capillaries and alveolus, and ameliorates cardiac, pulmonary and renal functions. Consequently, HVHF significantly lowered the APACHE II scores in SAP patients.

CRP is a pentameric protein with a molecular weight of 120 kDa synthesized by the liver. It promotes the production of inflammatory cytokines and enhances inflammatory response. Hence, CRP level reflects the strength of the inflammatory response induced by various factors (injury, infection and necrosis) in vivo, and serves as a sensitive and reliable index for the diagnosis, treatment, and monitoring of inflammatory responses. CRP is considered one of the key parameters for evaluating the severity of SAP.[30] After 3 days, CRP did not significantly decline after HVHF. However, at day 7, it significantly decreased and was close to normal values. This could be related to the elimination of inflammatory cytokines such as IL-1β and TNF-α, as well as the alleviation of inflammatory responses. The insignificant decrease observed at day 3 may be associated with the CRP peak after the initial insult.

It was reported that 50.9% to 76.3% of SAP cases die from MODS within 2 weeks of disease onset. Among these cases, 33.3% to 49.1% were due to concurrent infections.[31] Despite the great progress in intensive care and treatment during the past decades,[32] the incidence of SAP death remains high.[33] Blocking the reaction cascade by inflammatory mediators at the early stage and preventing infection has become the key in nonsurgery therapies to reduce death rates. As shown above, hemofiltration can help SAP patients undergo the acute phase smoothly, increase the treatment success rate, reduce surgical intervention rate, and shorten the length of hospitalization. Therefore, HVHF should be considered an important, effective, and safe treatment in the early stage SAP.

As for HVHF timing, once SAP is diagnosed, it should be performed as early as possible if no contraindications such as low blood pressure or severe bleeding tendency are present.[34] We believe that it is necessary to perform HVHF within 48 hours of SAP diagnosis in line with SIRS standards, in order to control inflammatory response, improve disease progression, prevent organ dysfunction or its progression, increase success rate of rescue, and reduce complications.

Finally, we compared the costs between both the control and HVHF groups, and found that there was no statistically significant difference; indicating that hemofiltration increases treatment value while maintaining its affordability.

Due to clinical trial and ethics limitations, the sample size of this trial was small; and we were unable to conduct a randomized controlled study. In addition, all patients were recruited and treated in the same center, with inherent bias. Therefore, these findings need to be confirmed in larger and multicenter studies.

In summary, the comparison between control and HVHF-treated patients revealed that hemofiltration is a promising supplement for the treatment of SAP. Indeed, HVHF efficacy and safety was demonstrated in this study, as well as its affordable cost. Therefore, further studies should assess the possibility of broadly using HVHF in clinic to better tackle SAP and similar pathologies.

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