

Original Article

Evaluation of the therapeutic effect of hemopurification in hyperlipidemic severe acute pancreatitis

Liangliang Hui¹, Ailiang Zeng², Xiangcheng Zhang¹, Kui Zang¹, Futai Shang¹

¹Department of ICU, The First People's Hospital of Huaian, Nanjing Medical University, Huaian 223300, Jiangsu, China; ²Department of Neurosurgery, The First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, Jiangsu, China

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Abstract: Background: To compare the therapeutic effects of continuous renal replacement therapy (CRRT), hemoperfusion with continuous venovenous hemofiltration (HP/CVVH) and plasma exchange with continuous venovenous hemofiltration (PE/CVVH) in hyperlipidemic severe acute pancreatitis (HLSAP). Methods: A total of 68 HLSAP patients underwent standard treatment for severe acute pancreatitis (SAP) in addition to CRRT alone (Group A), HP+CRRT (Group B), or PE+CRRT (Group C). Patient vital signs, Acute Physiology and Chronic Health Evaluation (APACHE) II scores, triglyceride (TG) levels, C-reactive protein (CPR) levels and the functional indices of vital organs before treatment were compared with these values 72 hours after treatment in each group. The changes in computed tomography severity index (CTSI) after one-week treatment were evaluated by CT examination. Results: No statistically significant differences were observed in APACHE II scores, serum amylase levels, or urine amylase levels among the three groups at 72 hours after treatment. Compared with Group A, the improvement in other laboratory parameters was more evident in Groups B and C. Meanwhile, Groups B and C patients showed significant much more reduction of CTSIs than group A patients after one-week treatment ($P < 0.05$). In the comparison of clinical status of the three groups, Groups B and C exhibited statistically significant improvement than Group A. Furthermore, compared with CRRT alone, CRRT in combination with HP or PE produced a quicker response in lowering the serum TG and cholesterol (CHO) levels and a reduced incidence of systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome/multiple organ failure (MODS/MOF). Conclusions: Compared with CRRT alone, CRRT in combination with HP or PE effectively produced better clinical outcome and lowered the mortality rate for patients with hyperlipidemic severe acute pancreatitis.

Keywords: Hyperlipidemic, severe acute pancreatitis, continuous renal replacement therapy, hemoperfusion, plasmapheresis

Introduction

Severe acute pancreatitis (SAP) is a life-threatening syndrome that can cause systemic inflammatory response syndrome (SIRS), sepsis, and even multiple organ dysfunction syndrome (MODS) [1, 2], with a mortality rate of up to 36-50%. Cholelithiasis, alcoholism and hyperlipidemia are the primary causes of acute pancreatitis (AP). According to the 2012 Revision of the Atlanta Classification of acute pancreatitis, the severity of AP is classified as mild, moderate, or severe [3]. In contrast to the low mortality rate of mild AP, severe AP not only has a high mortality rate but also has a high incidence of complications [4]. Thus far, many measures to treat AP have been employed in

clinical practice, including common surgical treatments, peritoneal lavage, supportive therapy for organ functions, endoscopic retrograde cholangiopancreatography, hemopurification, and other effective treatments. Despite these therapies, the treatment of SAP is still enormously challenging, and its mortality rate is still as high as 15-25% [5]. The incidence of SAP secondary to hyperlipidemia has increased significantly in recent years, and hyperlipidemia-induced SAP accounts for 12-38% of all SAP cases [6]. From January 1991 to December 2010, the number of hyperlipidemic acute pancreatitis (HLAP) cases increased by 1.5-fold, and the morbidity rate increased from 5.4% to 8.3%, with an average of 7.3%. A retrospective controlled study reported a morbidity rate of

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9.2% for HLAP. Among these patients were 62 cases of HLAP, accounting for 18.45% of patients with AP [7]. The age of onset of HLSAP is lower than that for biliary pancreatitis, with a higher rate of complications and more serious conditions. Reducing serum triglyceride (TG) concentrations as early as possible is required in HLSAP treatment. In recent years, our hospital adopted hemoperfusion with continuous venovenous hemofiltration (HP/CVVH) and plasma exchange with CVVH ((PE)/CVVH) for the treatment of HLSAP. Remarkable outcomes have been achieved with these measures. Based on the case information of the HLSAP patients who were admitted to the Department of Critical Care Medicine in our hospital since 2010, CRRT alone and CRRT in combination with HP were compared in terms of their effects on patient condition and prognosis.

Materials and methods

Study subjects

A total of 68 patients with HLSAP were recruited from the intensive care unit of our hospital from August 2010 to June 2016. The subjects included 41 men and 27 women, with a mean age of (40.9±8.5) years. Diagnostic criteria as listed: (1) The diagnosis of HLSAP was based on the Atlanta Classification [8] in the management of AP, published by the World Gastroenterology Organisation, while the diagnosis of SIRS and MODS was based on the guidelines recommended by the American College of Clinical Pharmacy (ACCP) [9] and Society of Critical Care Medicine (SCCM) [10]. (2) Serum TG levels were required to be greater than or equal to 11.30 mmol/L. (3) SAP cases induced by other causes were excluded. (4) Treatment with CRRT and (or) HP or PE was administered to the patients during hospitalization. The exclusion criteria were as follows: (1) incomplete clinical information; (2) hospital discharge against medical advice for reasons unrelated to disease; and (3) inability to be examined by CT due to critical conditions after hospitalization. The criteria for complete recovery from hyperlipidemia were as follows: (1) disappearance of the SAP symptoms; and (2) all test results within normal levels.

Experimental grouping

According to the different treatment methods, patients are divided into three groups: 23 CRRT

cases, 25 HP/CVVH cases and 20 PE/CVVH cases. Patients among three groups had no statistical significance in aspects of gender, age and BMI. Before the treatment, the above three kinds of treatments were introduced to patients and their families. According to decisions of the patients to choose treatment method, we analyzed the effect of three treatments.

Treatments for patients

The three groups were all treated with CRRT and standard therapies for AP (i.e., fasting and limited water intake, gastrointestinal decompression, fluid resuscitation, suppression of gastric acid secretion, suppression of pancreatic exocrine and inhibition of pancreatic enzyme secretion, anti-infection measures, organ function protection, nutritional support, symptomatic treatment and traditional Chinese medicine). CRRT was carried out by replenishing replacement fluid using the predilution method, with a blood flow rate of 150-220 mL/min and a replacement fluid flow rate of 30-50 mL/kg per hour. Sodium citrate (4%) was used as a local anticoagulant, and a 5% calcium chloride injection was supplemented after filtration. Filtration and arterial blood calcium levels were monitored every 4 hours to adjust for the levels of sodium citrate and calcium chloride. Post-filtration supplementation of 15-40 ug/kg of enoxaparin sodium (supplied by Sanofi-Aventis) was administered to patients with hypercoagulability, and the dosage was adjusted according to activated clotting time (ACT) and activated partial thromboplastin time (APTT) values (provided by HEMOCHRON® JrSignature+). CRRT filters and plate dialyzers were changed every 12.4±6.8 hours. The duration of continuous treatment was determined according to the patient's condition, with an average of 72-216 hours. The ultrafiltration volume was also determined based on the patient's condition. Before CRRT, the patients in Group B received HP for 2-2.5 hours using a Fresenius multiFiltrate CRRT machine, plate dialyzers, and a Zhuhai Jianfan hemoperfusion device with HA330 resin. Patients in Group C were treated with plasma exchange for 3-4 hours using a Fresenius multiFiltrate CRRT machine, plate dialyzers, and a PlasmaFLUX P2dry plasma separation device, with a replacement volume of 1,000 mL/h that was calculated according to the following formula: (kg)* (1-HCT).

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Table 1. Laboratory index of patients in three groups before and after 72 hours treatment ($\bar{x} \pm s$)

Group	Case No.	APACHE (Score)	TG (mmol/l)	WBC	CRP	Total CHO (mmol/l)	Serum amylase	
A	Before	23	16.51±4.03	21.53±6.69	14.01±3.75	156.1±37.38	20.70±7.65	758.96±151.26
	After	23	9.32±1.84	12.38±2.77	10.52±1.31	69.83±12.97	8.03±5.21	541.24±82.56
B	Before	25	17.48±3.36	22.23±7.36	13.98±1.45	149.78±31.65	21.24±8.12	726.91±131.24
	After	25	7.09±2.48	5.84±2.51	10.91±0.89	43.61±14.02	5.75±2.35	473.29±67.53
			P > 0.05	P < 0.001	P > 0.05	P = 0.027	P = 0.008	P > 0.05
C	Before	20	18.32±3.67	23.87±7.82	14.86±1.54	166.35±39.86	19.37±7.63	780.12±163.45
	After	20	7.12±2.32	4.86±2.32	9.98±0.81	48.64±14.62	5.27±2.98	432.24±58.62
			P > 0.05	P < 0.001	P > 0.05	P = 0.012	P = 0.010	P > 0.05
Group	Case No.	Urine amylase	PaO ₂ /FiO ₂	TB (μmol/l)	ALT (U/L)	Scr (μmol/l)	BUN (μmol/l)	
A	Before	23	3013.59±869.12	169.78±28.53	95.47±15.25	107.39±15.03	365.8±28.7	27.31±8.03
	After	23	1866.32±765.78	211.35±21.56	37.27±10.63	55.53±10.68	99.89±8.18	11.39±2.54
B	Before	25	2824.08±876.93	152.69±31.53	102.37±15.87	112.38±12.27	353.7±26.9	25.56±4.72
	After	25	1103.75±589.68	271.68±25.21	22.39±11.24	33.79±7.82	71.89±12.13	7.29±3.08
			P > 0.05	P = 0.009	P > 0.05	P = 0.008	P = 0.037	P = 0.026
C	Before	20	3012.43±871.54	148.12±30.56	90.53±14.23	129.63±14.21	363.2±28.4	27.87±8.01
	After	20	1103.46±586.65	280.65±27.23	20.14±9.68	32.87±6.92	68.56±11.36	7.28±3.02
			P > 0.05	P = 0.007	P > 0.05	P = 0.006	P = 0.012	P = 0.021

P-values are shown as B or C Group difference respectively when compared to the A group using repeated measured ANOVA.

Table 2. CTSI of patients in three groups before and after 2-week treatment ($\bar{x} \pm s$)

Group	Case No.	Before	After	P value
A	23	5.83±0.67	4.38±0.72	na
B	25	5.78±0.81	3.28±0.86	0.042
C	20	5.82±0.83	3.36±0.89	0.040

P-values are shown as B or C Group difference respectively when compared to the A group using repeated measured ANOVA.

Observational indicators and detection methods

A blood flow rate of 120-180 mL/min was used, and heparin was used as a standard anticoagulant. The monitored parameters primarily included (1) general parameters: APACHE II score, serum TG and CHO levels, incidence of major complications within 1 week after treatment, clinical conditions, and outcome; (2) inflammation indicators: WBC, and C-reactive protein (CRP); (3) pancreatitis-related parameters: serum and urine amylase; (4) major organ functional indicators: oxygenation index (PaO₂/FiO₂), total bilirubin (TB), alanine aminotransferase (ALT), serum creatinine (SCr) and blood urea nitrogen (BUN) levels before treatment and 72 hours after treatment; and (5) the CT Severity Index (CTSI).

Statistical analysis

All data were analyzed using SPSS 22.0. Measurement data are expressed as $\bar{x} \pm s$ and were compared using a t test. The two groups (A vs. B, B vs. C, or B vs. C) were compared in laboratory index (APACHEII score, TG, WBC, CRP, Total CHO, Serum amylase, Urine amylase, PaO₂/FiO₂, TB, ALT, Scr and BUN), CTSI, clinical situation and outcome using a t-test. The χ^2 tests were used to compare the constituent ratios in major complication occurrence or mechanical ventilation rate between the two groups. P values of χ^2 tests are performed for overall comparison of different treatment response among three groups. Partition χ^2 (A vs. B and C) tests are performed once there is significance identified. Differences were considered statistically significant at a value of P < 0.05.

Results

Patients treated with CRRT in combination with HP or PE show more apparent improvement in laboratory index changes

Before treatment, three groups of patients had no statistical difference in related index. However, three groups of patients showed a signifi-

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Table 3. Major complication of patients in three groups after 2-week treatment (%)

Group	ARDS (n%)	AKI (n%)	Pleural effusion (n%)	Abdominal cavity effusion (n%)	Acute peripancreatic effusion (n%)
A	16 (69.5)	9 (39)	16 (69.5)	17 (73.9)	12 (52.1)
B	5 (20)	7 (28)	14 (56)	15 (60)	11 (44)
C	4 (20)	7 (35)	10 (50)	14 (70)	10 (50)
χ^2 tests	0.033	0.844	0.793	0.895	0.941
Partition χ^2 (A vs. B and C)	0.009	Na	Na	Na	Na

P values of χ^2 tests for overall comparison among three groups. Partition χ^2 (A vs. B and C) tests are performed once there is significance identified.

Table 4. Clinical situation and outcome

Group	Mechanical ventilation (n%)	Mechanical ventilation time (d)	Abdominal pain relief time (d)	Anus exhaust time (d)	Case fatality rate (n%)	Hospital stays (d, $\bar{x} \pm s$)
A	15 (65)	9.13±2.23	5.48±1.59	5.48±1.59	7 (30)	33.61±5.63
B	5 (20)	5.33±1.93*	3.14±0.77*	3.14±0.77*	1 (4)	29.37±6.82*
C	4 (20)	5.48±1.98*	3.09±0.68*	3.21±0.84*	1 (5)	27.51±5.36*
χ^2 tests	0.049	Na	Na	Na	0.040	Na
Partition χ^2 (A vs. B and C)	0.014	Na	Na	Na	0.011	Na

P values of χ^2 tests for overall comparison among three groups. Partition χ^2 (A vs. B and C) tests are performed once there is significance identified. *P* value of T-tests for B or C groups when compared to the A group, **P* < 0.05.

cantly improved general index, inflammation index, pancreas related index and main viscera function indexes after treatments (*P* < 0.05). Patients in B and C group harbored a more apparent improvement in TG, CRP, Total CHO, PaO₂/FiO₂, ALT, Scr and BUN (*P* < 0.05). See **Table 1**.

Patients treated with CRRT in combination with HP or PE show more apparent improvement in CT severity

Patients in three groups showed obviously improved abdominal CT performance, and decreased CTSI (*P* < 0.05) after one-week treatment. Patients in B and C group showed significant improvement than those in group A (*P* < 0.05). There is no statistical difference between B and C group (*P* > 0.05). Shown in **Table 2**.

Patients treated with CRRT in combination with HP or PE show better clinical situation and outcome

The incidence of respiratory distress syndrome (ARDS) and acute renal failure in B and C group was lower than that in group A (*P* < 0.05). The incidence of chest and abdomen effusion and acute peripancreatic fluid between the two

groups had no statistical significance (*P* > 0.05). See **Table 3**. Patients in B and C group showed significant difference in general clinical situation, the case fatality rate and length of hospital stay in comparison with A group (*P* < 0.05). See **Table 4**.

Discussion

According to the Fredrickson classification, hyperlipidemic patients with serum TG levels greater than 11.3 mmol/L are more prone to SAP [11]. The pathogenesis of HLSAP has not been fully elucidated, although the currently accepted primary mechanism is the hydrolysis of TG by pancreatic lipase, leading to an increase in free fatty acids (FFA) in excess of the binding capacity of albumin. Excessive FFA levels directly damage gland cells and small blood vessels in the pancreas via cell membrane lipid peroxidation, inducing trypsinogen activation and pancreatic autodigestion and result in HLSAP. Meanwhile, excessive FFA levels induce acidosis, activate trypsinogen, and aggravate the pathological damages from pancreatitis. Hyperlipidemia is associated with hypercoagulability and hyperviscosity, making patients prone to thrombosis and impairing pancreatic microcirculation when coupled with obstruction

of the pancreatic microvasculature due to the accumulation of high serum lipid levels [12-14]. Hyperlipidemia activates platelets and in turn induces the release of a large amount of vasoconstrictive thromboxane. Meanwhile, the damage of pancreatic vascular endothelial cells reduces the secretion of vasodilative substances, such as prostacyclin, further aggravating the impairment of pancreatic microcirculation [15]. These mechanisms work together to induce pancreatic autodigestion, even ischemia and necrosis, leading to inflammation in the pancreas and the surrounding area. This increase in inflammation is characterized by the extravascular aggregation of inflammatory cells, such as neutrophils. These cells release proinflammatory cytokines, such as tumor necrosis factor- α , IL-6, and IL-8 [13, 16], causing a cascade of inflammatory responses and SIRS, which can further develop into MODS/multiple organ failure (MODS/MOF).

HLSAP patients exhibit abnormally elevated TG levels, which are positively correlated with the severity of HLSAP, with a mutual promotion effect. Therefore, the key factor in the treatment of HLSAP is a rapid reduction of TG levels. Our retrospective analysis also confirmed that early rapid reduction of TG levels significantly improved the clinical conditions, test results, outcomes and prognosis of the patients. Studies from other countries have also indicated that the progression of HLSAP ceases when serum TG levels are below 5.65 mmol/L. Therefore, in patients with HLSAP, early lipid-lowering treatment is the first choice for treating the disease [17]. A rapid reduction of serum TG levels can decrease the production of toxic FFA and prevent SIRS. Compared with SAP from other causes, HLSAP has the following onset characteristics: younger age, lower incidence of abdominal compartment syndrome, and faster stabilization of conditions following rapid lipid-lowering treatment. Our retrospective analysis suggests that the conventional CRRT is less effective in lowering blood lipid levels. However, other studies found that blood lipid levels were rapidly and significantly decreased after patients were treated with HP and plasma replacement in combination with CRRT, leading to early and effective control of SIRS and thus rapid remission.

The main principle of HP is to absorb macromolecules in the blood onto a sorbent with an

extremely large surface area when the blood passes through a perfusion device filled with the sorbent. This is a treatment method for the removal of endogenous or exogenous toxic substances in the blood followed by reinfusion of the blood. HP is characterized by its ability to remove substances of large molecular weight and high lipophilicity, as well as toxins or drugs that can bind to proteins. HP can effectively remove cytokines and inflammatory mediators in the blood, thereby inhibiting the inflammatory response, reducing damage to tissues and organs, and reconstituting a balanced immune environment in the body. HP combined with CRRT has been successfully used to treat pregnant patients with hyperlipidemic pancreatitis [18]. Serum levels of TG, cholesterol (CHO) and low-density lipoprotein (LDL) were significantly lowered after HP, with the most significant reduction observed in TG levels, suggesting that HP effectively removed lipids. When SAP patients received early HP+CRRT, their TNF- α , IL-1 and IL-6 levels were significantly decreased. Microcirculation was improved, homeostasis was rapidly achieved, and the overall prognosis was good. HP+CRRT treatment effectively removed TG and inflammatory factors and improved patient survival. Similar results were observed with patients in Group B in our study.

PE treatment has been shown to reduce serum TG levels and to prevent further aggravation of HLSAP in patients [19]. PE reduced the incidence of SAO in patients with severe hyperlipidemia who failed to respond to conventional treatment [20]. A recent study showed a decrease of 60% in serum TG levels within several hours after PE treatment [2]. A study showed a good therapeutic effect of PE in 11 HLSAP patients [12]. Stefanutti proposed the mechanism of PE for the treatment of HLSAP, including the removal of chylomicrons, the removal of proteases and proinflammatory factors in the blood, and the reduction of the hypersensitivity reaction [21].

The main issue with a single HP/PE treatment for HLSAP is the rebound of blood lipids and inflammatory factors and mediators. The primary reasons are the re-synthesis of these substances and their vascular entry from the extravascular space. HP or TPE treatment can be administered again upon rapid increase in intravascular concentration of these substances. These extravascular macromolecules will

be redistributed into blood vessels and can only be cleared when they enter the blood stream. It takes a long time for these extravascular macromolecules to be transported into blood vessels and to reach equilibrium; therefore, a satisfactory therapeutic effect can only be achieved when HP/PE treatment is given every 24-48 hours.

Compared with HP and PE, CRRT simulates the filtration and reabsorption mechanism of glomeruli, which can quickly correct electrolyte disturbances and acid-base imbalances and maintain homeostasis in vivo mainly through dispersion and convection diffusion to timely eliminate small- and medium-sized molecules, a rapid reduction in inflammatory factors in the internal environment at the time of SAP, regulation of immune functions, removal of part of the TG, alleviation of the inflammatory response, and prevention of the occurrence of SIRS and MODS/MOF [22].

Therefore, CRRT in combination with HP or PE is theoretically more effective than CRRT alone in the treatment of HLSAP. Our retrospective analysis also indicated that CRRT in combination with HP or PE more rapidly reduced the levels of blood lipids and inflammatory factors when compared with CRRT alone. These combination treatments more effectively blocked the occurrence of SIRS; significantly improved respiratory, liver and kidney functions; alleviated inflammation in the pancreas and peripancreatic tissues; effectively reduced the incidence of complications, such as acute respiratory distress syndrome (ARDS) and acute renal injury; improved patient prognosis; significantly reduced the morbidity and mortality rates of HLSAP; and shortened the length of patient hospital stays.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Futai Shang, Department of ICU, The First People's Hospital of Huaian, Nanjing Medical University, Huaian 223300, Jiangsu, China. E-mail: 827698416@qq.com

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