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Prolonged Intermittent Renal Replacement Therapy Combined with Hemoperfusion Can Improve Early Recovery of Moderate and Severe Acute Pancreatitis, Especially in Patients with Acute Kidney Injury

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Keywords
Acute pancreatitis · Prolonged intermittent renal replacement therapy · Hemoperfusion · APACHE II · Acute kidney injury

Abstract
Introduction: The aim of this study was to investigate the efficacy of prolonged intermittent renal replacement therapy (PIRRT) plus hemoperfusion (HP) in treating moderately severe acute pancreatitis (MSAP) and severe acute pancreatitis (SAP). ***Methods:*** A total of 105 MSAP and SAP patients were enrolled. Sixty of them received routine internal medical therapy (control group), and 45 received PIRRT and HP in addition to routine internal medical therapy (PIRRT + HP group). The vital signs, laboratory results, and the Acute Physiology and Chronic Health Evaluation II (APACHE II) score were compared between the two groups before treatment and on the 3rd and 7th days of treatment. ***Results:*** No deaths or treatment-related serious adverse reactions occurred in both groups. After 3 and 7 days of treatment, the APACHE II score decreased more significantly in the PIRRT + HP group than in the control group (3 days: 5.47 [±3.30] vs. 7.53 [±3.89], $p = 0.005$. 7 days: 4.82 [±3.49] vs. 6.87 [±3.54], $p = 0.004$). After 3 days of treatment, the inflammatory combination parameters systemic immune-inflammation index (SII) and neutrophil-to-lymphocyte ratio (NLR) in the PIRRT + HP group decreased more significantly than those in the control group (SII: 1,239.00 [737.80–1,769.00] vs. 2,013.00 [1,260.00–3,167.00], $p = 0.001$. NLR: 8.78 [±4.52] vs. 11.88 [±7.30], $p = 0.009$). After 7 days of treatment, SII, NLR, and hypersensitive C-reactive protein decreased significantly compared with baseline, but no statistical differences between the two groups were observed. AST in both groups remained stable with treatment. There was no significant difference in baseline creatinine between the two groups of AKI patients, but after 3 and 7 days of treatment, the proportion of acute kidney injury (AKI) patients in the PIRRT + HP group whose creatinine decreased by 50% from baseline or fell to the normal range was significantly higher than that in the control group ($p < 0.05$). ***Conclusion:*** PIRRT + HP therapy could not only improve the general conditions, as measured by APACHE II score, but also reduce the inflammatory cascade of patients with acute pancreatitis. For MSAP and SAP patients complicated with AKI, this therapy may accelerate the recovery of renal function.

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Introduction

Acute pancreatitis (AP) is an inflammatory disease of the pancreas, which is characterized by edema, bleeding, and necrosis caused by various mechanisms [1]. With the improvement of living standards and changes in diet, the incidence of pancreatitis is gradually increasing. The 2012 Atlanta classification standard divides acute pancreatitis into three severity levels (mild acute pancreatitis, moderately severe acute pancreatitis [MSAP], and severe acute pancreatitis [SAP]) [2]. The onset and progression of acute pancreatitis is rapid. The release of a large number of inflammatory mediators in the early stage may lead to systemic inflammatory response syndrome and inflammatory cell infiltration in important organs (such as the lung, liver, and kidney), which aggravates organ damage, and further results in multiple organ dysfunction syndrome [3, 4].

So far, many therapeutic strategies have been developed for the pathogenesis of AP. In addition to medical treatment, surgical treatment, and interventional therapy, blood purification treatment is also one of the effective treatment methods. Continuous venous-venous hemofiltration (CVVH) is one of the most commonly used blood purification procedures for critically ill patients, and it can effectively regulate the volume, acid-base, and inhibition of inflammatory cascade reaction [5]. Although it has possible benefits, CVVH has several disadvantages in clinical application, including intensive nursing requirements, large human and material investment, and high medical costs. Recently, prolonged intermittent renal replacement therapy (PIRRT) has been proposed as intermediate forms of therapy between continuous and intermittent renal replacement therapy [6]. At present, there is no clear and unified definition of PIRRT. Broadly speaking, any in vitro renal replacement therapy mode given intermittently for a long time (≥6 h) can be defined as PIRRT [6]. Clinical trials have generally demonstrated that PIRRT is noninferior to continuous renal replacement therapy regarding patients' outcomes [7, 8].

In recent years, hemoperfusion (HP) based on adsorbents has been proposed to eliminate cytokines in the blood. Due to the filtration membrane material and pore size, the removal of larger molecules such as inflammatory cytokines by CVVH is limited, but resin adsorbent can solve this problem. Resin adsorption HP can remove macromolecules, exceeding the molecular weight cutoff value of the CVVH filtration membrane [9]. The combination of PIRRT and HP (PIRRT + HP) exhibits enhanced mediator clearance and theoretically would be more effective for AP. This study retrospectively analyzed the clinical data of 105 AP patients to explore the efficacy and results of PIRRT combined with HP in the treatment of AP and to provide a new blood purification strategy for clinical treatment.

Patients and Methods

Patients

A total of 105 patients with MSAP and SAP treated in Tongji Hospital Affiliated with Tongji Medical College, Huazhong University of Science and Technology (Wuhan, China) from January 2018 to May 2021 were collected, of which 60 were treated with routine medical treatment (control group), and 45 patients were supplemented with PIRRT and HP for 3–5 cycles on the basis of routine internal medical treatment (PIRRT + HP group). The use of PIRRT plus HP was prescribed by the doctor-in-charge according to his/her clinical experiences. Before PIRRT + HP treatment, all patients received detailed information about the advantages and disadvantages of PIRRT + HP treatment and provided written informed consent.

Inclusive criteria: (1) patients met the 2012 Atlanta diagnostic criteria for MSAP and SAP [2]; (2) patients who were older than 18 years old; (3) patients who had acute and continuous abdominal pain; and (4) CT detection grades were D (peripancreatic exudation) and E (pancreatic necrosis and abscess). Exclusion criteria: (1) patients with digestive system diseases caused by other reasons; (2) patients with severe heart, liver, and kidney disorders; (3) pregnant or lactating women; (4) patients with pancreatic cancer; and (5) patients who were younger than 18 years old. The protocol of the present study complied with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Tongji Hospital Affiliated to Tongji Medical College, Huazhong University of Science and Technology (No.TJ-IRB20211131).

Methods

Routine Internal Medical Therapy

Vital signs of patients were closely detected, and all patients received controlled fluid resuscitation, fasting, gastrointestinal decompression, acid suppression and enzyme suppression, antispasmodic pain relief. Nutritional support was initially started with total parenteral nutrition, which was later combined with enteral feeding as soon as gastrointestinal peristaltic movement was confirmed. Provide respiratory support based on blood gas analysis results and respiratory status, and use ventilator to assist ventilation when necessary. If there are clear signs of intrapancreatic and extrapancreatic infection, quinolones (moxifloxacin or levofloxacin) and nitroimidazoles (ornidazole) in combination with β-lactam antibiotics (carbapenems or third-generation cephalosporins) were used.

PIRRT and HP Procedures

In addition to internal medical therapy, patients in the PIRRT + HP group underwent 3–5 cycles of PIRRT + HP treatment. Each cycle included 6–8 h of daytime CVVH and 2 h of HP. PIRRT + HP treatment began within 48 h of admission. After 3–5 cycles of blood purification, patients continued to receive internal medical

treatment until discharge. The use of blood purification treatment was determined by the doctor-in-charge and with the informed consent of the patients.

Daytime CVVH (PIRRT) was carried out using a multiflorane hemofiltration machine (Fresenius, Germany) with an AV1000s polysulfide membrane filter (Fresenius, Germany). By means of the Seldinger technique, the femoral or right internal jugular vein was punctured to place a single-needle catheter with a double lumen for temporary vascular access. Blood flow through the circuit was set at 180–250 mL/min, and the substitution fluid was infused at a rate of 4 L/h with a combination of predilution and postdilution (4:1). The filter circuit was prewashed with heparin-saline. The flow speed of preflush was approximately 100 mL/min. Substitution fluid consisted of sodium 140 mmol/L, calcium 1.5 mmol/L, magnesium 0.75 mmol/L, chloride 110 mmol/L, bicarbonate 35 mmol/L, and glucose 10 mmol/L (Qingshan Likang Pharmaceutical Co., Ltd., Chengdu, China). The amount of ultrafiltration was determined according to the daily volume of fluid replacement and physiological requirement. Heparin anticoagulation was given to patients without diffuse intravascular coagulation or bleeding tendency according to their coagulation function, the first dose of 20–40 mg, maintained at 2–5 mg/h, and patients with bleeding tendency were given citric acid anticoagulant therapy or heparin-free dialysis.

HA330 or HA330-II (Zhuhai Jafron biomedical materials Co., Ltd., Zhuhai, China) was used for 2 h of HP before PIRRT, which was installed before the hemofilter with a blood flow of 150–200 mL/min. The HP device was connected in series before the hemofilter. After 2 h of treatment, the HP device was removed, and the daytime CVVH treatment was continued.

Data Collection

All information was obtained and managed through established data collection forms. We reviewed the demographic data, clinical records, and laboratory results (including routine blood tests, blood biochemistry, coagulation function, and blood gas analysis) of all enrolled patients. During the treatment, patients' vital signs such as heart rate (HR), body temperature, respiratory rate, and blood pressure were monitored in real time. Laboratory results were recorded before treatment (0 day), on the third and seventh day of treatment, and the Acute Physiology and Chronic Health Evaluation II (APACHE II) score at these three time points were calculated to evaluate the severity of patients. All laboratory test results of the PIRRT + HP group were collected before blood purification treatment. All data were checked by two physicians (Xi Yang and Chunyu Pan).

Definition

Acute kidney injury (AKI) is defined as one of the following conditions: (1) serum creatinine increased ≥0.3 mg/dL (≥26.4 μmol/L) within 48 h. (2) Serum creatinine rises to greater than 1.5 times baseline within 7 days. (3) Urine volume less than 0.5 mL/(kg·h) for 6 h.

Neutrophil-to-lymphocyte ratio (NLR) refers to the ratio of neutrophil count to lymphocyte count in peripheral blood. Systemic immune-inflammation index (SII) was calculated with the formula SII = (P × N)/L, where P, N, and L refer to peripheral platelet, neutrophil, and lymphocyte counts, respectively.

Statistical Analyses

GraphPad Prism 8 (GraphPad Software, USA) and SPSS 23.0 (IBM Corporation, Armonk, NY, USA) were used for statistical analysis and visualization. To show the normal distribution of variables, the Kolmogorov-Smirnov test was used. Continuous parametric data were expressed as the mean (standard deviation), and the *t* test or one-way ANOVA followed by Tukey's multiple comparison test was used for univariate comparisons. Continuous nonparametric data were expressed as the median (interquartile range), and the Mann-Whitney U test or Kruskal-Wallis test followed by Dunn's multiple comparison test was used for univariate nonparametric comparisons. Categorical data were expressed as frequencies (percentages), and the χ^2 test or Fisher's exact test was used to compare variables. Two-tailed $p < 0.05$ was considered statistically significant.

Results

Comparison of Baseline Data between the Two Groups

Table 1 shows the baseline characteristics of patients in the study and control groups. There were no significant differences between the PIRRT + HP group and the control group in gender composition, mean age, mean arterial pressure, APACHE II score, primary diseases, and etiology of pancreatitis. In laboratory test results, except for HR, hemoglobin, and hematocrit (HCT), there were no significant differences in baseline characteristics between the two groups. The reason for the differences in these parameters may be that in clinical treatment, patients in the PIRRT + HP group were more severe than those in the control group. Even after matching the parameters such as age and the APACHE II score, there were still differences in some parameters between the two groups at baseline (Table 1).

Comparison of Biochemical Parameters of the PIRRT + HP Group before and after Treatment

The results showed that after 3–5 cycles of PIRRT + HP treatment, mean arterial pressure, serum sodium, alanine aminotransferase, aspartate aminotransferase, and activated partial thromboplastin time (APTT) were stable, and there were no significant differences compared with baseline. The APACHE II score, which reflects the severity of AP, decreased from 9.51 (±4.62) to 5.56 (±3.15) after treatment, and the difference was statistically significant ($p < 0.001$). The average HR decreased significantly from 111.50 (±18.90) bpm to 95.91 (±13.07) bpm ($p < 0.001$). Among the indicators of inflammation, hypersensitive C-reactive protein (hsCRP) decreased from 219.8 (104.10–295.70) mg/L to 146.70 (107.30–196.60) mg/L ($p = 0.016$), interleukin-6 (IL-6) decreased from

Table 1. Demographics and clinical characteristics of patients in the PIRRT + HP group and control group

Parameters	PIRRT + HP	Control	*p* value
N	45	60	–
Male, *n* (%)	26 (57.80)	29 (48.30)	0.338[a]
Age, years	46.93 (±12.78)	50.80 (±15.17)	0.170[c]
MAP, mm Hg	95.53 (±17.99)	97.50 (±13.52)	0.542[c]
HR, bpm	111.50 (±18.90)	98.95 (±17.87)	0.001[c]
APACHE II score	9.51 (±4.62)	9.08 (±3.81)	0.604[c]
MSAP, *n* (%)	13 (28.89)	18 (30.00)	0.902[a]
SAP, *n* (%)	32 (71.11)	42 (70.00)	0.902[a]
Cause of disease			
Cholelithiasis, *n* (%)	26 (57.70)	37 (61.60)	0.687[a]
Hyperlipidemia, *n* (%)	15 (33.30)	37 (61.60)	0.687[a]
Alcoholism, *n* (%)	4 (8.80)	6 (10.00)	1.000[a]
Others, *n* (%)	0 (0.00)	5 (8.30)	0.128[a]
Primary disease			
Hypertension, *n* (%)	13 (28.80)	16 (26.60)	0.801[a]
Diabetes mellitus, *n* (%)	14 (31.10)	16 (26.60)	0.618[a]
Heart disease, *n* (%)	5 (11.10)	8 (13.30)	0.732[a]
Cerebrovascular disease, *n* (%)	2 (4.40)	2 (3.30)	1.000[a]
Others, *n* (%)	4 (8.80)	8 (13.30)	0.479[a]
Laboratory findings			
White blood cell count, 10^9/L	14.33 (11.73–18.73)	12.50 (10.18–16.59)	0.114[b]
Hemoglobin, g/L	148.00 (124.50–165.50)	130.00 (98.00–153.00)	0.005[b]
HCT, %	42.29 (±6.99)	37.91 (±8.72)	0.007[c]
Platelet, 10^9/L	210.00 (162.50–245.30)	218.00 (163.00–269.00)	0.716[b]
ALT, U/L	17.00 (12.00–57.50)	22.00 (13.00–74.00)	0.229[b]
AST, U/L	30.00 (20.00–50.50)	31.00 (17.00–52.00)	0.926[b]
Serum albumin, g/L	34.53 (±5.56)	35.43 (±6.53)	0.460[c]
Serum creatinine, μmol/L	81.00 (53.00–102.50)	68.00 (51.75–102.80)	0.560[b]
Blood urea nitrogen, mmol/L	6.05 (3.45–9.68)	5.20 (3.26–7.68)	0.270[b]
Total cholesterol, mmol/L	4.76 (3.78–9.90)	4.23 (3.07–7.64)	0.107[b]
Triglyceride, mmol/L	3.98 (1.22–22.89)	2.17 (0.94–10.75)	0.090[b]
Serum potassium, mmol/L	4.19 (3.90–4.58)	4.05 (3.61–4.40)	0.140[b]
Serum sodium, mmol/L	136.00 (131.90–138.20)	135.60 (134.00–138.30)	0.440[b]
Serum calcium, mmol/L	1.87 (±0.30)	1.97 (±0.29)	0.079[c]
Bicarbonate, mmol/L	19.40 (17.50–22.90)	20.60 (16.60–23.00)	0.775[b]
APTT, s	37.60 (33.23–41.08)	39.90 (35.00–44.90)	0.079[b]
D-dimer, μg/mL	3.78 (1.88–6.56)	3.36 (1.40–6.74)	0.782[b]
hsCRP, mg/L	219.80 (104.10–295.70)	152.60 (81.00–268.50)	0.326[b]
IL-6, pg/mL	158.40 (70.05–291.00)	133.40 (51.92–328.30)	0.564[b]
Serum amylase, IU/L	469.50 (125.30–1,021.00)	230.30 (105.60–1,148.00)	0.637[b]

Values are expressed as mean (±SD), median (25–75th percentile), or *n* (%). IQR, interquartile range; APACHE II, Acute Physiology and Chronic Health Evaluation II; AKI, acute kidney injury; HCT, hematocrit; ALT, alanine aminotransferase; AST, aspartate aminotransferase; APTT, activated partial thromboplastin time; IL-6, interleukin-6; hsCRP, hypersensitive C-reactive protein; MAP, mean arterial pressure. [a] χ^2 test. [b] Mann-Whitney U test. [c] *t* test.

158.40 (70.05–291.00) pg/mL to 16.76 (2.72–23.49) pg/mL ($p = 0.001$), and HCT decreased from 42.29% (±6.99%) to 35.79% (±5.13%) ($p < 0.001$).

After treatment, the patients' hemoglobin, platelet, albumin, creatinine, total cholesterol, serum potassium, and serum amylase were significantly decreased. There may be three reasons for the reduction of albumin: (1) abnormal albumin metabolism caused by inflammation, (2) insufficient albumin intake, and (3) plasma protein loss through the filter caused by hemodialysis [10]. In addition, D-dimer increased from 3.78 (1.88–6.56) μg/mL to 7.15 (4.80–10.19) μg/mL after treatment. The above

Table 2. Comparison of biochemical parameters before and after 3–5 cycles of treatment in the PIRRT + HP group

Parameters	Before treatment	After treatment	*p* value
N	45	45	–
MAP, mm Hg	95.53 (±17.99)	96.89 (±13.11)	0.684[b]
HR, bpm	111.50 (±18.90)	95.91 (±13.07)	<0.001[b]
APACHE II score	9.51 (±4.62)	5.56 (±3.15)	<0.001[b]
Laboratory findings			
White blood cell count, 10^9/L	14.33 (11.73–18.73)	13.21 (9.39–17.64)	0.174[a]
Hemoglobin, g/L	148.00 (124.50–165.50)	118.00 (107.50–131.00)	<0.001[a]
HCT, %	42.29 (±6.99)	35.79 (±5.13)	<0.001[b]
Platelet, 10^9/L	210.00 (162.50–245.30)	180.00 (117.00–220.00)	0.018[a]
ALT, U/L	17.00 (12.00–57.50)	20.00 (13.00–31.00)	0.763[a]
AST, U/L	30.00 (20.00–50.50)	27.00 (22.25–42.75)	0.690[a]
Serum albumin, g/L	34.53 (±5.56)	30.30 (±3.77)	<0.001[b]
Serum creatinine, μmol/L	81.00 (53.00–102.50)	63.00 (48.00–71.00)	0.002[a]
Blood urea nitrogen, mmol/L	6.05 (3.45–9.68)	5.52 (3.70–7.62)	0.252[a]
Total cholesterol, mmol/L	4.76 (3.78–9.90)	3.40 (2.84–4.50)	<0.001[a]
Triglyceride, mmol/L	3.98 (1.22–22.89)	2.73 (1.41–4.17)	0.156[a]
Serum potassium, mmol/L	4.19 (3.90–4.58)	3.84 (3.66–4.30)	0.012[a]
Serum sodium, mmol/L	136.00 (131.90–138.20)	136.70 (134.70–139.30)	0.082[a]
Serum calcium, mmol/L	1.87 (±0.30)	2.00 (±0.17)	0.014[b]
Bicarbonate, mmol/L	19.40 (17.50–22.90)	23.50 (22.30–25.10)	<0.001[a]
APTT, s	37.60 (33.23–41.08)	39.60 (35.80–42.60)	0.154[a]
D-dimer, μg/mL	3.78 (1.88–6.56)	7.15 (4.80–10.19)	0.001[a]
hsCRP, mg/L	219.80 (104.10–295.70)	146.70 (107.30–196.60)	0.016[a]
IL-6, pg/mL	158.40 (70.05–291.00)	16.76 (2.72–23.49)	0.001[a]
Serum amylase, IU/L	469.50 (125.30–1,021.00)	48.00 (34.00–81.00)	<0.001[a]

Values are expressed as mean (±SD), median (25–75th percentile), or *n* (%). IQR, interquartile range; APACHE II, Acute Physiology and Chronic Health Evaluation II; HCT, hematocrit; ALT, alanine aminotransferase; AST, aspartate aminotransferase; APTT, activated partial thromboplastin time; IL-6, interleukin-6; hsCRP, hypersensitive C-reactive protein; MAP, mean arterial pressure. [a] Mann-Whitney U test. [b] *t* test.

results showed that PIRRT combined with HP could improve the general condition of AP patients and was an effective treatment strategy (Table 2).

Comparison of Data between the Two Groups after 3 and 7 Days of Treatment

The changes of the APACHE II score and serum biochemical parameters in two groups before and after 3 and 7 days of treatment are shown in Table 3. APACHE II is used to evaluate the severity of AP. Before treatment, APACHE II scores of the two groups were markedly increased, with an average of more than 8 points, and the difference was not statistically significant ($p = 0.604$). APACHE II scores of the two groups decreased gradually with treatment, but the PIRRT + HP group decreased more significantly. After 3 days of treatment, the APACHE II score decreased from 9.51 (±4.62) to 5.47 (±3.30) in the PIRRT + HP group and from 9.08 (±3.81) to 7.53 (±3.89) in the control group. On the 7th day, patients in the PIRRT + HP group had finished 3–5 cycles of blood purification procedures more than 48 h, but the APACHE II score of the PIRRT + HP group was still significantly less than that of the control group (4.82 [±3.49] vs. 6.87 [±3.54], $p = 0.004$) (Table 3; Fig. 1).

SII and NLR are two combined inflammatory parameters, which can reflect the state of systemic inflammation. After 3 days of treatment, SII in the PIRRT + HP group decreased more significantly than that in the control group (1,239.00 [737.80–1,769.00] vs. 2,013.00 [1,260.00–3,167.00], $p = 0.001$), and NLR in the PIRRT + HP group also decreased more significantly than that in the control group (8.78 [±4.52] vs. 11.88 [±7.30], $p = 0.009$). After 7 days of treatment, SII, NLR, and hsCRP decreased significantly compared with baseline, but no statistical differences between the PIRRT + HP group and the control group were observed (Table 3).

As for liver function, aspartate aminotransferase in both groups remained stable with treatment. At 3 and 7

Table 3. Comparison of data between the two groups after 3 and 7 days of treatment

Parameters	PIRRT + HP ($N = 45$)			Control ($N = 60$)		
	0 day	3 days	7 days	0 day	3 days	7 days
APACHE II	9.51 (±4.62)	5.47 (±3.30)[a,b]	4.82 (±3.49)[a,b]	9.08 (±3.81)	7.53 (±3.89)[a]	6.87 (±3.54)[a]
HR, bpm	111.50 (±18.90)[b]	92.62 (±16.01)[a]	86.93 (±12.67)[a]	98.95 (±17.87)	96.07 (±19.00)	85.76 (±16.94)[a]
HCT, %	42.29 (±6.99)	37.08 (±11.45)[a,b]	35.32 (±4.72)[a]	37.91 (±8.72)	33.70 (±5.87)	34.28 (±6.32)[a]
hsCRP, mg/L	219.80 (104.10–295.70)	146.70 (106.20–213.30)	85.80 (43.23–136.10)[a]	152.60 (81.00–268.50)	176.70 (91.75–241.00)	71.35 (32.50–144.80)[a]
NLR	15.63 (±9.17)	8.78 (±4.52)[a,b]	9.16 (±6.34)[a]	14.76 (±8.92)	11.88 (±7.30)	8.34 (±5.28)[a]
SII	2,867.00 (1,893.00–4,063.00)	1,239.00 (738.00–1,769.00)[a, b]	2,132.00 (1,062.00–3,733.00)	2,665.00 (1,783.00–3,771.00)	2,013.00 (1,260.00–3,167.00)[a]	1,928.00 (1,008.00–3,239.00)[a]
ALT, U/L	17.00 (12.00–57.50)	19.00 (11.00–29.00)	19.00 (12.00–24.00)	22.00 (13.00–74.00)	17.00 (10.00–38.00)	16.00 (10.00–36.00)
SCr, μmol/L	81.00 (53.00–102.50)	63.00 (48.75–73.00)[a]	59.50 (47.75–70.25)[a]	68.00 (51.75–102.80)	60.0 (49.0–95.25)	63.50 (50.75–92.25)
HCO_3^-, mmol/L	19.40 (17.50–22.90)	23.95 (22.48–25.13)[a]	25.15 (23.38–28.03)[a,b]	20.60 (16.60–23.00)	22.65 (20.03–25.45)[a]	23.90 (20.63–26.73)[a]
BUN, mmol/L	6.05 (3.45–9.68)	5.39 (3.13–7.38)	4.37 (3.18–5.97)[a]	5.20 (3.26–7.68)	5.36 (4.08–7.31)	5.13 (3.54–7.50)
APTT, s	37.60 (33.23–41.08)	39.90 (36.73–42.45)[b]	38.50 (35.40–42.65)	39.90 (35.00–44.90)	43.60 (39.65–46.13)[a]	42.30 (36.95–45.00)
D-dimer, μg/mL	3.78 (1.88–6.56)	7.28 (4.95–10.86)[a]	7.90 (4.91–10.15)[a]	3.36 (1.40–6.74)	5.55 (3.54–11.20)[a]	4.96 (3.93–10.10)[a]
Serum amylase, IU/L	469.50 (125.30–1,021.00)	61.00 (35.50–95.50)[a]	56.00 (28.00–78.00)[a]	230.30 (105.60–1,148.00)	72.50 (44.00–145.30)[a]	63.00 (30.75–100.00)[a]

APACHE II, Acute Physiology and Chronic Health Evaluation II; HR, heart rate; HCT, hematocrit; hsCRP, hypersensitive C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; SII, Systemic Immune-Inflammation Index; ALT, alanine aminotransferase; HCO_3^-, bicarbonate; BUN, blood urea nitrogen; APTT, activated partial thromboplastin time. [a]Identifies these variables differ significantly from their baseline value. [b]Identifies these variables differ significantly from the control group.

Color version available online

Fig. 1. Comparison of the APACHE II score between the two groups before and after treatment (**$p < 0.005$).

days of treatment, creatinine in the PIRRT + HP group decreased from 81.00 (53.00–102.50) μmol/L to 63.00 (48.75–73.00) μmol/L and 59.50 (47.75–70.25) μmol/L, with statistically significant differences from baseline ($p = 0.006$, $p = 0.006$), while creatinine in the control group showed no difference from baseline after treatment ($p = 0.525$, $p = 0.644$). On the 7th day, although the blood purification treatment had ended, the bicarbonate level in the PIRRT + HP group was still significantly higher than that in the control group (25.15 [23.38–28.03] mmol/L vs. 23.90 [20.63–26.73] mmol/L, $p = 0.015$) (Table 3).

The APTT of patients in the PIRRT + HP group were within the normal range (29–42 s) before and after treatment without significant fluctuation, while the APTT of patients in the control group increased significantly after 3 days of treatment (43.60 [39.65–46.13] vs. 39.90 [35.00–44.90], $p = 0.025$), and the median value of APTT in the control group exceeded the upper limit of the normal range after 3 and 7 days of treatment. The D-dimer in both groups increased after treatment, and the D-dimer of the PIRRT + HP group was slightly higher than that of the control group at three different times, but the differences were not statistically significant (Table 3).

Parameters that differed significantly at baseline were compared by calculating differences before and after treatment. Compared with the control group, HR, HCT, and hemoglobin decreased faster in the PIRRT + HP group after 3 and 7 days of treatment, and serum calcium increased more in the PIRRT + HP group after 7 days of

Table 4. Comparison of parameters with large baseline differences between the two groups

Parameters	PIRRT + HP (n = 45)	Control (n = 60)	p value
HR, bpm			
0 day	111.50 (±18.90)	98.95 (±17.87)	0.001
Δ3 days	15.00 (4.00–26.50)	5.00 (–8.00 to 17.75)	<0.001
Δ7 days	25.00 (14.75–36.50)	15.00 (1.00–27.00)	0.003
HCT, %			
0 day	42.29 (±6.99)	37.91 (±8.72)	0.007
Δ3 days	6.50 (1.80–10.40)	3.20 (0.25–6.25)	0.049
Δ7 days	6.70 (1.50–12.60)	2.15 (–0.80 to 6.55)	0.009
Hemoglobin, g/L			
0 day	148.00 (124.50–165.50)	130.00 (98.00–153.00)	0.005
Δ3 days	25.00 (5.50–49.50)	13.00 (1.00–26.00)	0.033
Δ7 days	25.50 (6.50–49.50)	9.00 (0.75–27.00)	0.007
Serum calcium, mmol/L			
0 day	1.87 (±0.30)	1.97 (±0.29)	0.079
Δ3 days	–0.09 (–0.26 to 0.06)	0.00 (–0.16 to 0.09)	0.153
Δ7 days	–0.20 (–0.37 to –0.02)	–0.09 (–0.23 to 0.07)	0.043

Values are expressed as mean (±SD), median (25–75th percentile), or n (%). HCT, hematocrit; Δ3 days, difference between 0 days of data minus 3 days of data; Δ7 days, difference between 0 days of data minus 7 days of data.

Table 5. Renal function recovery of patients with AKI in the two groups after treatment

Parameters	PIRRT + HP	Control	p value
AKI, n (%)	16 (35.56)	19 (31.67)	0.676
3 days get well,* n (%)	14 (87.50)	9 (47.37)	0.030
7 days get well,* n (%)	14 (87.50)	10 (52.63)	0.035

* Get well refers to the reduction of creatinine by 50% from baseline or below the upper line of the normal range (female: <84 μmol/L, male: <104 μmol/L).

treatment (p = 0.043). In addition, compared with baseline, the HR and HCT decreased significantly after 3 days of treatment in the PIRRT + HP group, while differences did not occur until 7 days of treatment in the control group (Table 4).

Comparison of Data between the Two Groups Complicated with AKI

There was no difference in the rate of AKI between the PIRRT + HP group and the control group (35.56% vs. 31.67%, p = 0.676). A total of 16 patients in the PIRRT + HP group were in AKI stages 1–3 (stage 1: n = 12 [75.00%], stage 2 and 3: n = 4 [25.00%]), and a total of 19 patients in the control group were in AKI stages 1–3 (stage 1: n = 11 [57.89%], stage 2 and 3: n = 8 [42.11%]). After 3 days of treatment, creatinine of the AKI subgroup in the PIRRT + HP group was able to return to normal range more rapidly or decrease by 50% from baseline more rapidly than the control subgroup (87.50% vs. 47.37%, p = 0.030). On the 7th day, although the blood purification treatment had ended, the improvement rate of renal function in the PIRRT + HP group was still significantly higher than that in the control group (87.50% vs. 52.63%, p = 0.035) (Table 5). Consistent with these results, the decrease of creatinine in the PIRRT + HP group was more significant than that in the control group. There was no significant difference in creatinine between the two subgroups at baseline (p > 0.05). After 3 and 7 days of treatment, creatinine in the PIRRT + HP subgroup decreased more significantly than that in the control subgroup (Table 6).

There was no difference in the APACHE II score between the two subgroups at baseline (p > 0.05). After 3 days of treatment, the APACHE II score in the PIRRT + HP subgroup decreased from 12.56 (±5.22) to 6.81 (±3.43), significantly less than 9.26 (±3.80) in the control group (p < 0.05). After 7 days of treatment, the APACHE II score of the PIRRT + HP subgroup was less than 8 points, but the control subgroup was more than 8 points (7.00 [±4.10] vs.8.74 [±3.48]) (Fig. 2). As for inflammatory indexes hsCRP, NLR, and SII, both sub-

Table 6. Comparison of data between the two groups complicated with AKI

Parameters	PIRRT + HP ($N = 45$)			Control ($N = 60$)		
	0 day	3 days	7 days	0 day	3 days	7 days
APACHE II	12.56 (±5.22)	6.81 (±3.43)[a,b]	7.00 (±4.10)[a]	11.26 (±4.11)	9.26 (±3.80)	8.74 (±3.48)
HR, bpm	114.90 (±24.91)[b]	90.44 (±19.19)[a]	89.73 (±13.16)[a]	97.68 (±18.78)	99.84 (±24.16)	91.22 (±21.96)
BUN, mmol/L	10.35 (6.44–13.22)	6.61 (4.45–9.67)	5.60 (4.48–7.63)[a]	9.00 (5.91–19.10)	9.70 (6.20–11.10)	7.26 (5.00–8.98)
SCr, μmol/L	110.50 (100.30–160.50)	67.00 (55.25–86.00)[a,b]	66.00 (51.50–101.30)[a,b]	143.00 (105.00–258.00)	133.00 (88.00–161.00)	113.00 (79.00–131.00)
HCO_3^-, mmol/L	19.43 (±3.80)	23.68 (±3.42)[a]	25.33 (±3.32)[a,b]	18.77 (±3.84)	21.83 (±3.27)	21.51 (±6.84)
hsCRP, mg/L	193.80 (55.25–293.60)	172.70 (129.70–210.20)	88.05 (44.93–128.80)	177.00 (57.65–278.60)	170.70 (42.45–270.30)	146.20 (84.10–186.20)
NLR	15.01 (±7.47)	10.42 (±4.62)	11.43 (±7.10)	14.53 (±9.06)	11.51 (±8.44)	9.57 (±5.98)
SII	2,987.00 (2,597.00–3,748.00)	1,405.00 (876.00–1,730.00)[a]	2,075.00 (1,647.00–3,097.00)	2,579.00 (1,470.00–4,163.00)	1,516.00 (745.6–3,003.00)	1,658.00 (901.70–3,669.00)
TVU, mL	1,181.00 (±521.80)	2,087.00 (±1,046.00)[a]	2,369.00 (±1,096.00)[a]	1,294.00 (±708.20)	2,376.00 (±733.70)[a]	2,126.00 (±775.20)[a]

APACHE II, Acute Physiology and Chronic Health Evaluation II; HR, heart rate; BUN, blood urea nitrogen; SCr, serum creatinine; $HCO3^-$, bicarbonate; hsCRP, hypersensitive C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; SII, Systemic Immune-Inflammation Index; TVU, total volume of urine in 24 h. [a]Identifies these variables differ significantly from their baseline value. [b]Identifies these variables differ significantly from the control group.

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Fig. 2. Comparison of the APACHE II score before and after treatment in the two groups of patients complicated with AKI (*$p < 0.05$).

groups decreased with treatment, but there were no significant differences between the two subgroups (Table 6).

Complications and Survival

During the treatment, there was no death in both groups. The main adverse reactions during blood purification treatment are allergies, hypotension, bleeding, pneumothorax and filter clotting. In our blood purification treatment, no patients experienced allergic reactions, pneumothorax or bleeding. Four patients had transient hypotension during blood purification treatment. In addition, 2 patients had filter blockage during blood purification treatment and needed to be replaced. More importantly, none of these adverse events resulted in severe consequences, which guaranteed the safety of PIRRT and HP for AP patients.

Discussion

Acute pancreatitis is a heterogeneous disease ranging from the minimal inflammation seen in mild interstitial pancreatitis to the extensive pancreatic necrosis and multisystem organ failure of severe attacks [11]. However, one-fifth of patients develop severe disease, with a mortality rate of approximately 20% [1, 12]. Leukocyte overactivation and cytokine cascade reaction are considered to be the important causes and pathogenesis of systemic

inflammatory response syndrome, multiple organ dysfunction syndrome, and even death in SAP, especially the inflammatory cascade in the early stage of AP is a key link affecting the development of AP [4]. Therefore, early treatment can further inhibit the inflammatory cascade and theoretically improve the prognosis of AP. Previous studies have shown that early preemptive application of blood purification therapy is safe and effective in the treatment of SAP [13, 14]. In our study, when patients had no remission under drug treatment and were at risk of further aggravation, we performed blood purification treatment according to the clinical experience of the attending physicians. It was not because of the single factor of elevated creatinine that patients received blood purification treatment but because of the continuous aggravation of symptoms such as abdominal pain and abdominal distension, serious infection, and unstable general vital signs. Although the patients did not develop severe AKI at this time, blood purification treatment was performed, which we called early intervention. Our study showed that early application of PIRRT combined with HP is a safe and feasible treatment scheme for AP, which could early reduce the critical illness score of patients and avoid further aggravation and deterioration of the disease.

To date, this is the first study to present the use of PIRRT combined with HP in the treatment of moderate to severe acute pancreatitis. Our study showed that early PIRRT combined with HP for 3–5 cycles could significantly improve the critical illness score of patients with MSAP and SAP. After 3 and 7 days of treatment, the APACHE II score decreased more significantly in the PIRRT + HP group than in the control group. Even though the blood purification treatment had ended on the 7th day, the APACHE II score of PIRRT + HP group was still significantly less than that of the control group. Recently proposed combinations of these systemic inflammatory parameters, including NLR and SII, reflect the systemic inflammatory state of the body and are associated with the prognosis of critical diseases [15, 16]. In this study, NLR and SII of the PIRRT + HP group were significantly less than those of the control group on the third day of treatment, suggesting that our blood purification therapy could improve the systemic inflammatory state of patients with moderate and severe pancreatitis. However, on the 7th day after treatment, there was no statistical difference in inflammatory indicators between the two groups, which may be due to the fact that the included patients only received PIRRT and HP treatment for 3–5 cycles due to economic reasons. If the treatment continues, more significant therapeutic effects may be observed. For the subgroups of patients with AKI in both groups, after 3 days of treatment, the proportion of patients in PIRRT + HP subgroup whose creatinine decreased by 50% from baseline or fell to the normal range was significantly higher than that in the control subgroup, and the proportion was also significantly higher than that in the control subgroup on the 7th day, even though the blood purification treatment had been stopped on the 7th day. On the third day, the decrease of serum creatinine may be related to the ongoing blood purification treatment, but more than 48 h after the end of blood purification treatment, serum creatinine of the AKI subgroup in the PIRRT + HP group was still significantly less than that of patients in the control subgroup. Therefore, we consider that PIRRT and HP therapy may accelerate the recovery of renal function.

In recent years, blood purification has played an increasingly important role in the treatment of critical diseases with its unique advantages. In addition to effectively controlling the patient's fluid balance and correcting acid-base imbalance, CVVH can also remove small- and medium-molecular-weight solutes through convection and at the same time absorb some large-molecular solutes through the filtration membrane [5, 17]. Therefore, the application of CVVH in the treatment of AP and its complications, and the removal of medium and large molecular inflammatory mediators, has become an important theoretical basis and key for successful treatment. However, the adsorption capacity of blood filter membrane is limited, so it is difficult to completely remove inflammatory factors, and the removal rate decreases significantly with longer blood-membrane contact. Levels of tumor necrosis factor-α, IL-6, and other inflammatory cytokines are significantly reduced after 6 h of treatment. This scavenging rate significantly decreases after 8 h of treatment, reaching almost zero after 12 h [18]. PIRRT adopts 6–8 h of short-term intermittent treatment, which can prevent the low filtration efficiency caused by filter saturation and microthromboembolism during 24-h CVVH treatment.

Classic CVVH involves continuous 24-h renal replacement therapy, which is a time-consuming, labor-intensive, and expensive treatment. During continuous 24-h CVVH treatment, the filter may cause inefficient filtration due to saturation and microthromboembolism. In our study, patients with moderate to severe pancreatitis received CVVH treatment mainly during the daytime, and this allowed the patients to achieve sufficient rest at night and provide functional rehabilitation and time for restoration of immune balance under pathological condi-

tions [19]. More importantly, daytime CVVH prevents low filtration efficiency due to filter saturation and microthromboembolism during 24-h CVVH treatment.

Different from the conventional dose, we used a substitution fluid flow rate of 4 L/h. Ronco et al. [20] found that increasing the amount of substitution fluid per unit time increased the number of inflammatory mediators cleared by the filter, thus enhancing the clearance effect of convection and promoting the contact between inflammatory mediators and filtration membranes, further enhancing the adsorption effect of filtration membranes. Jiang HL et al. [13] found similar results, and they found that the flow rate of substitution fluid at 4 L/h in CVVH treatment was more effective in removing inflammatory mediators such as TNF-α, IL-1β, and IL-6 than that of 1 L/h. Therefore, increasing the filtration rate can increase the adsorption mass and prolong adsorptive saturation time of filter membranes. Therefore, according to other research and clinical experience, we used a substitution fluid flow rate of 4 L/h, which may increase the clearance of interleukin and TNF-α. In addition, we combined HP on the basis of daytime CVVH and achieved good results. The HA-type HP device uses a neutral macroporous adsorption resin as an adsorbent, which can adsorb medium and large molecules of cytokines and inflammatory factors [9] so as to make up for the shortcomings of CVVH. Previous studies have found that CVVH combined with HP can clear various inflammatory mediators more effectively than CVVH alone [21]. Li et al. [22] also suggested that CVVH combined with HP could better remove toxic metabolites and inflammatory mediators in SAP than HP alone, and it not only shortens the time of symptoms disappearing but also decreases the incidence of complications and the mortality. Based on clinical experience and previous studies, PIRRT combined with HP (PIRRT + HP) is theoretically more effective in treating AP.

There are some limitations in this study. This is a retrospective study in nature that might bring about bias of patient selection and also incompleteness of some important patients' clinical information. In addition, the sample size of this study is also limited. In clinical work, we collected several SAP patients who were treated with daytime CVVH on the basis of medical treatment, and it was observed that the effect was better than that of patients treated with medical drugs only. However, the were was limited and could not be included into groups for comparative analysis. In the future, more data are needed to compare the efficacy and prognosis of internal medical therapy alone, PIRRT therapy, and PIRRT combined with HP in patients with AP.

Conclusion

Early application of PIRRT combined with HP is a safe and feasible treatment scheme for AP, which can reduce early the critical illness score of patients and avoid further aggravation and deterioration of the disease. For patients with AP complicated with AKI, it can accelerate the recovery of renal function.

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Statement of Ethics

The study protocol and waived written informed consent were approved by the Medical Ethics Committee of Tongji Hospital Affiliated to Tongji Medical College, Huazhong University of Science and Technology (No.TJ-IRB20211131).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Junhua Li and Hao Pan designed the study. Meiling Gong, Xi Yang, and Chunyu Pan collected the data. Meiling Gong drafted the manuscript. Meiling Gong and Junhua Li were responsible for the data integrity and analysis. Yong Ning and Hao Pan critically reviewed the manuscript. All the authors provided significant inputs for data collection, intellectual content, and final approval.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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