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Research Article

Effect of Coupled Plasma Filtration Adsorption on Inflammatory Mediators and Liver Function of Patients with Severe Acute Pancreatitis

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Abstract

Background: To study the effect of coupled plasma filtration adsorption (CPFA) on the inflammatory mediators and liver function of patients with severe acute pancreatitis (SAP). Nowadays, CPFA is widely used in the therapy for patients with septicopyemia and septic shock and the outcome is better. However, its role in inflammatory mediators and the liver function of SAP patients are poorly understood.

Method: 46 patients with severe acute pancreatitis (SAP) were randomly divided into the CPFA group and the control group .The control group received conventional treatment in ICU, while the CPFA group received CPFA therapy besides conventional treatment for 3-10days. The changes of inflammatory mediators and liver function index before treatment and after treatment for 4 days and 8 days was determined.

Results: Compared with the control group, the serum level of TNF-α, IL-1, IL-6 and liver function index (AST, ALT, R-GT and total bilirubin) were decreased and the serum level of

IL-10 was increased in the CPFA group patients in 4th days and in 8th days. and the difference between the two groups was statistically significant ($p< 0.05$).

Conclusions: CPFA therapy can effectively reduce serum levels of TNF-α, IL-1, IL-6, and increase serum level of IL-10 and protect the liver function in SAP patients, and also improve overall body conditions. The study indicated that CPFA could be improving the clinical manifestations and eliminating inflammatory mediators and protection of liver function. It could be proved safe and feasible and an adjunctive therapy for SAP patients.

Keywords: The pair plasma filtration adsorption; Severe acute pancreatitis; Inflammatory mediators; Index of liver function

Introduction

Severe acute pancreatitis (SAP) is a kind of common and severe clinical disease in digestive department. It's clinical features including quick onset, severe conditions, more complications, and high mortality. SAP is often accompanied by Systemic Inflammatory Response Syndrome (SIRS) or even Multiple Organ Failure Syndrome (MOFS), having recurrent attacks due to alcohol abuse, overeating or biliary tract disease [1]. Patients should be hospitalized in Intensive Care Unit (ICU) and received complex therapy and kindly monitors. Coupled Plasma Filtration Adsorption (CPFA) is a new blood purification technology in current years designed for acute and severe patients combining various blood purification forms included blood filtration, plasmapheresis, plasma absorption and etc. Since low-flow haemodialysis does not allow the elimination of substances with a molecular weight exceeding 5 kDa, the removal of high molecular weight proteins such as myoglobin requires high volume hemodiafiltration techniques [2]. CPFA is an extracorporeal therapy which uses a plasma filter to separate plasma from blood, allowing the separated plasma to pass through an adsorbent cartridge for nonspecific removal of several mediators. After purification, plasma is returned to blood, which can then pass through a hemofilter for further purification by means of conventional haemodialysis, hemofiltration, or hemodiafiltration in case of acute Severe Pancreatitis (SAP). In a 28-day clinical observation, many studies included Colomina-Climent found that the infection rate of patients with septic shock declined by 20% after using plasma adsorption purification system [3]. The main therapeutic goal of CPFA is to hit the excess of pro- and anti-inflammatory mediators, in order to reestablish a normal balance and recover organ function [4]. CPFA increases the clear scope of macromolecule toxins, middle molecule toxins and micro molecule toxins to protect the functions of patients' organs. The study is based on conventional treatment of SAP, observing the effect of CPFA on inflammatory mediators and liver function of patients with SAP. The results are reports as follows.

Patients and Methods

Patients from January 2018 to December 2018, 46 patients with SAP admitted to Intensive Care Unit (ICU) of Binzhou hospital of Binzhou Medical University (Binzhou, China). The 46 patients were enrolled in the study and the inclusion criteria were diagnosed under the 2012 revision of the Atlanta classification. A patient was diagnosed upon the presence of at least two of the three following symptoms: consistent abdominal pain with acute pancreatitis (acute onset and persistent and severe and epigastric pain); serum lipase or amylase activity at least three times greater than the upper reference limit; and the characteristic findings of acute pancreatitis on contrast-enhanced computer tomography or magnetic resonance imaging or transabdominal ultrasonography [5]. The exclusion criteria were endocrine or metabolic disorders, immune insufficiency, cardiac, hepatic, renal or respiratory dysfunction, a history of radiotherapy or treatment with immuno-suppressive drugs and a terminal state, or lack of consent. Finally, 46 patients (27 males and 19 females) with a mean age of 41.5 years (range 21-74 years) were included in the study. All patients were continuously monitored for heartbeat rate, respiration rate, Mean Arterial Pressure (MAP), and oxygen saturation in the ICU.

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The Acute Physiology And Chronic Health Evaluation II (APACHE II) score and the Multiple Organ Failure (MOFS) were used to assess the severity of illness and predicted the effect of treatment. Patients were divided into the CPFA group and the control group with 23 patients respectively by the random number table. The two groups were both treated with conventional treatments, including fluid infusion, acid suppression, gastrointestinal decompression, gastric mucosa protection, antibiotics, pancreatic exocrine inhibition and Enteral Nutrition (EN) support as well as were monitored intensively. Based on the conventional treatment, the control group was administered HIGH FLOW BLOOD PERFUSION (HFBP) at the same time and the CPFA group was administered the Pair Plasma Filtration Adsorption (CPFA) technology. There was no significant difference between the two groups on etiology, APACHEП score, complication, age, gender, immunity, nutritional status and the severity of the disease ($p>0.05$). The two groups were comparable as show in Table 1.

Methods

The CPFA group based on the conventional treatment, patients with SAP applied CPFA technology and Seldinger method to construct vascular access by puncturing right jugular internal vein or applying double-lumen catheter in femoral vein. We applied ACH-10 multi-functional blood purification machine (Japanese Asahi Kasei medical company), PF 2000 plasma separator (Gambro, polypropylene film, 0.35 m^2), HA330 neutral macroporous resin absorber (Jafron Biotechnological company), F6 hem dialyzer (Fresenius dialysis machine company, Germany). In the beginning of CPFA therapy, blood flow increased gradually from 30~40 ml/min to 100~180 ml/min. Use dilation method to supplement replacement fluid after consuming it: the flow rate of replacement fluid was 2000~4000 ml/h and all treatment would not be suspended during the therapeutic process. During the process of CPFA therapy, change an absorber per 5 h (HA-330, Zhuhai lizhu medical biological material company) and absorb plasma to avoid its loss when changing absorber: change quickly and abide by aseptic principles, new absorber needed to be prewashed and closed by heparin saline for 30 minutes, use saline to wash off heparin saline before using and then insert in the circuit to complete extracorporal adequate anticoagulation and reduce heparin dosage. During the process of absorption, monitor the pressure difference before and after using absorber closely. If the pressure after absorber was too low, it showed blood clots in absorber and if the pressure after absorber was too high, it showed possibility of blood clots or obstruction happened in the downward blood pipe. We started lead blood treatment after adequate prewashing for 30 minutes by 0.9% normal saline 2000 ml and normal heparin 80 mg. At the beginning of therapy, the first dose of heparin was 3-10 mg and additional dose was 1-5 mg/h and they were input continuously by infusion pump for 8-10 h per treatment, lasting 3-10 days. The CPFA equipment was divided into two parts: one part was plasma separation and plasma adsorption for adsorbing endotoxin and medical mediator; the other part was hemodiafiltration for clearing excessive fluid and mini-molecular toxin. After eliciting through the deep vein, plasma was separated from the blood and affluxes the original blood after blood absorber and then was filtered by the blood filtration. The process of CPFA technology was as followed as Figure 1.

CPFA was different from pure blood replacement. A dialyzer was sidely jointed into the blood route after plasma separator and an absorber was sidely jointed into the plasma. We would not only observe the plasma separator itself, but also observe closely on the operation of absorber and dialyzer. The pressure change of any part had possibility for soaring of transmembrane pressure so that resulting in the rupture of membranes or the cease of plasma separating. Given the positive evolution of clinical course and lab- oratory values, CPFA was stopped and the patients were transferred from ICU to the digestive department for continuation of hospital cure and care procedure.

The control group While during the conventional treatment, patients with SAP applied traditional blood purification system; applied double chamber catheter (right subclavian vein or femoral vein) to draw blood; applied anticoagulation with low molecular heparin to make APTT prolong 1.5~2 times. Use QUARIUSA blood purification machine, plasma separator (MPS05, BELLCO S.R.L, Italy), blood filter (RENAFLO II, type HF1200), maximum transmembrane pressure 500mmHg, effective membrane area 1.25 m^2, hemoperfusion device (HA330-II, Zhuhai jianfan biotechnology co. LTD), substitution flow2000ml/h. The frequency of blood purification was based on patients' conditions and the course of treatment.

Monitoring SAP patients' vital signs (temperature, pulse, respiratory, blood pressure, bleeding and clotting time, etc.) and the entire operation of machines (pressure on tubes, blood leakage, hemolysis, rupture of membranes, blood clotting, obstruction, etc.). If something wrong happened, reducing the blood flow rate or ceasing therapy should be done according to the patients' condition. At the same time, other vital signs should also be monitored closely, including the input pressure, output pressure, transmembrane pressure, blood flow, the use of anticoagulation drug therapy. We should also observe SAP patient's

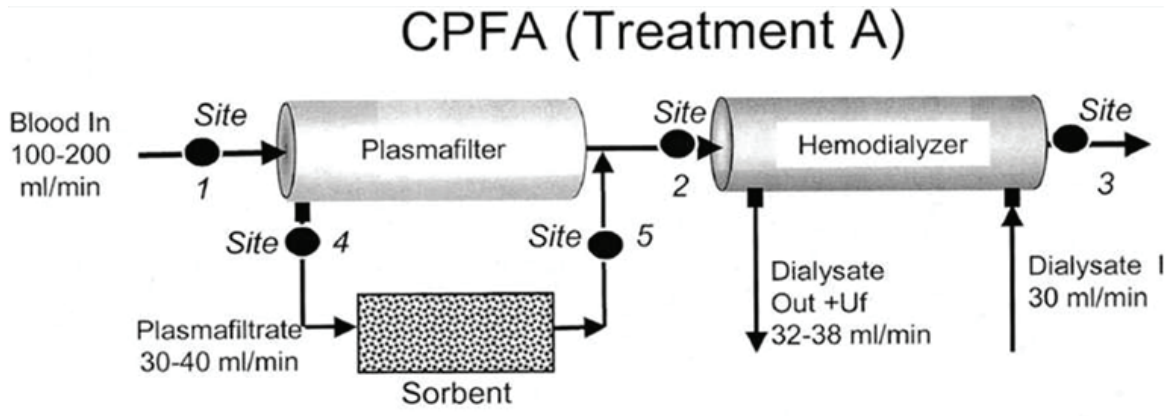

Figure 1: CPFA procedure.

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Table 1: The data of SAP patients on admission (n=46).

Patients information	Control group	CPFA group
Etiology (n)		
Biliary pancreatitis (n=21)	12	11
Overeat (n=18)	7	9
Anything else (n=7)	4	3
APACHEII score (score)	27	28
Complication (n)		
Infection	17	18
MOFS	9	10

Table 2: Comparison of effects between two groups in 8th days (n, %).

Indicator	control group	CPFA group
Remission of abdominal pain and distension (h)	44-37	31-41 *
Recovery of hemodiastase and urine amylase (h)	49-78	45-63*
APACHEII evaluation (score)	17-25	14-21*
Infection [n (%)]	11 (47.83)	7 (30.43)*
Complication [n (%)]	9 (39.13)	5 (21.74)*
Recovery [n (%)]	18 (78.26)	21 (91.31)*

Notes: Compared with control group *p<0.05

other vital signs including blood recovery time of amylase, abdominal pain, abdominal distension remission time and complications (pancreatic cyst, peritonitis, pseudocyst, MODS, septicemia.).

Detecting serum level of cytokines and liver function blood sample was abstained when patients with SAP were admitted into ICU on the first day, the fourth day and the eighth day; detect hematopoietic factors with Enzyme-Linked Immunosorbent Assay (ELISA) such as detecting the serum levels of TNF-α, IL-1, IL-6 and IL-10; detect serum level of hepatic function (ALT, AST, r-transglutaminase albumin and total bilirubin). In this study, serum level of liver function indexes (ALT, AST, R-GT and total bilirubin) had no differences before treatment in two groups. These results suggested that the cytokines and the liver function and Triacylglycerol might be difference between two groups in 4th days and in 8th day in SAP patients after therapy.

Statistical Analysis All data are presented as mean±standard deviation and analyzed by SPSS 19.0 statistical software. Statistical evaluation was performed by Student's t-test. All cytokine data were analyzed by one-way analysis of variance (ANOVA). A p-value <0.05 was considered statistically significant.

Ethical Considerations this study received approval from the Ethics Committee of Binzhou Medical University. Informed consent was obtained according to procedures approved by both the University's Research Board and the Human Volunteers Protection Committee. All of the participants gave their written informed consent for participation. All of the participants' information was kept confidential and anonymous.

Results

Therapeutic effect the therapeutic effect of the CPFA group was obviously better than that of control group. The differences including recovery rate, complication rate, infection rate, abdominal pain, abdominal distension remission time, recovery of hemodiastase and urine amylase and APACHEII score were significant than that of control group in 8th days (p<0.05), Table 2.

Table 3: The index of cytokines and liver function between two groups (±s).

Indicator	CPFA group	control group
TNF-α (ng/L)		
Before therapy	576.98±161.71	574.46±164.89
Therapy for 4 days	323.75±144.69*	494.79±173.54
Therapy for 8 days	79.31±46.75*	145.39±168.69
IL-1 (ng/L)		
Before therapy	49.81±14.63	49.27±14.29
Therapy for 4 days	26.24±11.36 *	39.16±12.33
Therapy for 8 days	12.76±10.39*	18.97±11.78
IL-6 (ng/Ll)		
Before therapy	397.63±163.67	396.46±168.41
Therapy for 4 days	225.47±114.82*	271.66±127.56
Therapy for 8 days	77.48±41.69*	101.43±55.43
IL-10 (ng/L)		
Before therapy	6.23±6.13	6.29±6.35
Therapy for 4 days	11.29±7.34 *	8.46±8.32
Therapy for 8 days	14.74±6.49*	11.52±8.95
WBC (109/L)		
Before therapy	27.13±6.56	27.89±7.61
Therapy for 4 days	14.22±9.35 *	18.65±8.93
Therapy for 8 days	10.41±3.17*	13.57±5.91
AST (u/L)		
Before therapy	388.61±10.76	388.59±10.81
Therapy for 4 days	222.59±13.56 *	267.24±13.57
Therapy for 8 days	110.76±10.39*	149.65±12.91
ALT (u/L)		
Before therapy	425.36±101.32	425.65±101.91
Therapy for 4 days	215.65±55.71 *	249.42±55.27
Therapy for 8 days	139.16±33.35 *	215.65±53.91
R-GT (ug/ml)		
Before therapy	29.36±10.32	29.65±10.91
Therapy for 4 days	21.75±7.71 *	24.72±7.96
Therapy for 8 days	13.16±3.75 *	16.65±3.91
Total bilirubin (ug/ml)		
Before therapy	29.36±11.32	29.65±11.91
Therapy for 4days	13.65±7.71 *	17.42±8.26
Therapy for 8days	7.16±5.35 *	13.65±6.97
Triacylglycerol (mmol/L)		
Before therapy	35.36±7.56	35.69±7.74
Therapy for 4 days	17.69±5.71 *	22.47±6.61
Therapy for 8 days	5.76±5.57 *	11.61±3.99

Notes: Compared with control group * p<0.05
*AST: aspartate aminotransferase; ALT: alanine aminotransferase; R-GT: R-Glutamine transpeptidase.

Comparison of serum level of cytokines and liver function between two groups, show in Table 3. Before treatment, there were no significant difference of the serum levels of cytokines and liver function between two groups. However, in the CPFA group, the serum levels of cytokines and liver function and triacylglycerol were significantly different than that of control group in 4th days and in 8th days.

Discussion

Severe Acute Pancreatitis (SAP) is a kind of hypermetabolic disease,

normally combined with systemic inflammatory response and it's vulnerable to lead to MODS related to liver with mortality at above 20% [5]. Treating patients with SAP is not only beneficial to clear cytokines in toxin and medium molecular substance, but also keep a balance on water, electrolyte and acid-base and keep homeostasis. Vital signs of patients in the CPFA group recovered gradually; the functions of liver got improved greatly. Severe complications didn't take place such as blood coagulation, hemorrhage, allergy, shock.

CPFA, a new type of continuous blood purification, combines a variety of mechanisms of blood purification therapy, and in particular reinforces, the adsorption mechanism shows a good prospect in the treatment of SAP patients.

Therapeutic effect of patients with SAP In recent years, as for pathological and physiological changes of MODS, the breakthrough was the discovery of multiple cytokines and related inflammatory mediators. Nowadays, being verified by researches, inflammatory reaction and immune dysfunction are the central link of MODS's happening and developing. The distinctive aspect of CPFA is the application of the sorbent to the plasma rather than the whole blood. This feature brings important benefits: the lower flow of plasma allows a prolonged contact with the sorbent and reduces biocompatibility issues [6]. Experience with the use of CPFA in Severe Acute Pancreatitis (SAP), especially about the effect on liver function and cytokines, is very limited. Lai et al. reported the successful use of CPFA in two kidney transplant patients with post-nephrolithotomy septic shock and severe rhabdomyolysis of unknown origin [7]. Ronco suggests the use of absorption on whole blood directly or CPFA, in which the patient's plasma is rein fused once regenerated by passage through a sorbent cartridge [8]. CPFA therapy is suitable to any patients with severe conditions combined with liver dysfunction and is especially fit for patients with advanced age, hypertension or cardiopulmonary dysfunction, postoperative trauma and bleeding tendency. It could clear inflammatory cytokines and some drugs in the systemic circulation and maximize rescue success rates of patients with hyper metabolism, Acute Renal Failure (ARF), heart failure, severe pancreatitis, adult respiratory distress syndrome and MODS, becoming a major therapeutic method for acute and severe patients [9].

SAP patients' anti-inflammatory function was improved Consecutive blood purification is a therapeutic method to clear water and solute in the body effectively and clear inflammatory mediator and cytokines through the adsorption of filtration membrane so that achieve the outcome to cure SAP. CPFA is an up-to-date method for blood purification and it combines many principles of blood purification therapy, especially the increase of the adsorption mechanism. The level of inflammatory factors in circulation is closely related to patients' prognosis. Massive inflammatory factors generated accelerate Systemic Inflammatory Response Syndrome (SIRS), Compensatory Anti-Inflammatory Response Syndrome (CARS) and Mixed Anti-Inflammatory Response Syndrome (MARS) so that lead to immunosuppression and imbalance of internal environment and generate a series of pathophysiology changes and dynamic changes in severity of conditions [10]. By regulating the generation of inflammatory factors, anti-inflammatory and proinflammatory functions reach equilibrium and immune homeostasis is recovered and new methods are probably provided for preventing MODS and improving prognosis [11]. Tumor Necrosis Factor Alpha (TNF-α) is an important inflammatory factor to attend SIRS and MODS. It plays an important part in the happening and development of SIRS by initiating a cascade of inflammation and participating in tissue cell damage and participating in hypermatabolism after trauma and activating the coagulation system and complement system. Body injured tissues express an array of inflammatory cytokines, including interleukin-1 (IL-1), tumor necrosis factor alpha (TNF-α), and interleukin-6 (IL-6). The rapid production and release of a large number of inflammatory cytokines can cause excessive local and systemic inflammation and lead to Systemic Inflammatory Response Syndrome (SIRS) and even cause Multiple Organ Dysfunction Syndrome (MODS) [12]. The removal of inflammatory cytokines may be remarkably enhanced and the anti-inflammatory cytokines such as interleukin-10 (IL-10) increased in the serum level. And the clinical manifestations could be improved using CPFA technology of SAP patients.

Maintain balance of water and electrolyte and acid-base and protection of liver function CPFA combined conventional therapy can not only clear cytokines and medium molecular substance in the body, but also maintain water and electrolyte acid-base balance [13]. Because of severe conditions, patients were accurately record the quantity of displacement liquid, percolate, dialysate, ultrafiltrate, drainage fluid, liquid intake and etc. We should monitor the changes of blood electrolyte and blood gas and regulate the quantity of electrolyte in displacement liquid or dialysate according to electrolyte condition, so as to do personal therapy [14]. In a CPFA therapy for 21 patients with septic shock, many experts included Matteo Franchi found that CPFA could increase patients' mean arterial pressure and decrease the demand for vascular activity and protect kidney function and enable patients' white cells increase or decrease and end up with tending to the normal range [15]. CPFA could not only maintain water and electrolyte acid-base balance as well as keeping the internal environment stable and protecting liver function, but also could regulate inflammatory/anti-inflammatory cytokines balance in serum and rebuild immune homeostasis [16]. In CPFA group, we began treatment with CPFA technology during conventional therapy, our patients showed a positive trend of clinical improvement and recovery better than that of control group ($p<0.05$). However, there were also some limitations for our study. First, all data were obtained from a single hospital. Whether our findings can be extended to the general population remains in doubt. Second, because of the relatively small sample size of SAP patients, statistical significance in our study should be interpreted with caution.

Conclusion

This study showed CPFA therapy could both decrease inflammatory mediators such as serum level of TNF-α, IL-1, IL-6 and increase serum level of IL-10 and also decrease serum level of glutamic-pyruvic transaminase, total bilirubin, Aspartate Aminotransferase (AST); Alanine Aminotransferase (ALT) and triacylglycerol and protection of liver function. The serum level of triacylglycerol declined obviously and electrolytes and acid–base metabolism balance were well maintained in the CPFA group. In addition, no therapy-related adverse reactions were found, so that the CPFA therapy could be proved safe and feasible and an adjunctive therapy for SAP patients.

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