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ORIGINAL PAPER

Hemodiafiltration Combined with Resin-Mediated Absorption as a Therapy for Hyperlipidemic Acute Pancreatitis

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Abstract The aim of this study is to investigate whether hemodiafiltration combined with resin-mediated absorption is a better therapy for hyperlipidemic acute pancreatitis. Patients ($n = 67$) with acute pancreatitis treated in ICU from January 2009 to December 2012 were included in this study. Seven of these 67 cases were diagnosed hyperlipidemic acute pancreatitis (HLAP). All the 7 HLAP patients went through fast, gastrointestinal decompression, anti-shock treatment, inhibition of pancreatic secretion, antiseptic treatments, and hemoperfusion (HP) combined with continuous veno venous hemodiafiltration (CVVHDF). After one round of treatment by resin adsorption, there was a significant decrease in serum triglycerides (TG) (29.78 %) and total cholesterol (TC) (24.02 %) levels ($p < 0.01$). TG and TC levels dropped by 49.02 and 37.66 %, respectively, after 1-day treatment of HP + CVVHDF; by 62.81 and 47.37 % on day 2 post-treatment; and by 69.57 and 49.47 % on day 3 post-treatment. All the 7 patients survived. The average time spent in the ICU was 7 ± 3.8 days, and the average duration of hospitalization was 19 ± 15.1 days. Our results show that hemoperfusion combined with hemodiafiltration is an efficient treatment as this approach can reduce plasma lipid levels effectively and reduce the risk of acute pancreatitis due to hyperlipidemia.

Keywords Hyperlipidemia · Acute pancreatitis · Resin adsorption · Hemodiafiltration

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Introduction

Acute pancreatitis (AP) is a severe medical condition that is often seen in the clinic. It is often associated with an increased incidence of multiple organ dysfunction. AP augments mortality rate considerably, due to the acute nature of this hyperinflammation that rapidly becomes exacerbated beyond effective treatment. Several major causes leading to AP include biliary disorder, over consumption of alcohol, intake of large amounts of food in a short period of time, and hyperlipidemia. In recent years, elevated quality of life has led to changes in dining habits in China, which correlates with an increased incidence of hyperlipidemia. As a consequence, the higher rates of hyperlipidemia have resulted in higher incidence of AP; AP caused by hyperlipidemia is termed as hyperlipidemic acute pancreatitis (HLAP). HLAP is occurring in the population now more frequently than ever before, and thus it has gained unprecedented attention from the physicians, researchers, and other members of the medical community. Xuanwu Hospital, Capital Medical University conducted a retrospective control study with 979 cases of AP and found that 9.2 % of these cases were HLAP [1]. The 2nd Surgical Department of Nankai Hospital treated 336 cases of AP between March 2007 and February 2010, among which there were 62 cases of HLAP (18.45 %) [2]. The most effective way to treat HLAP is to reduce plasma triglyceride (TG) levels quickly [3] and block inflammation as early as possible. It was reported that HLAP would not worsen if plasma TG levels were decreased to less than 5.65 mmol/L [4]. In our investigation, we combined hemoperfusion and hemodiafiltration therapy to treat HLAP patients. Beneficial outcomes such as reduced lipid levels, improved physical condition, and better prognosis were found when using this approach. The details of our study design and findings are reported as follows.

Patient Inclusion

The HLAP diagnostic criteria used for this study were: (1) the presence of clinical manifestations of acute pancreatitis; (2) plasma TG level $\geq$ 11.3 mmol/L, or 5.6–11.3 mmol/L but with visible fat suspension in the serum, at the time of admission; (3) and radiographic evidence of pancreatitis (such as CT or ultrasound). Cases of AP caused by biliary disorders, over intake of alcohol, medications, tumors, trauma, and causes other than hyperlipidemia were excluded. From January 2009 to December 2012, 67 cases with severe AP were accepted in the ICU, of which 7 cases matched the HLAP criteria (all cases had necrotic pancreatitis, which was ascertained by CT). The age of these 7 patients was between 32 and 47 years (mean 44.7), 6 were male and 1 was female. The APACHE score was $\geq$8 and the Ranson score was $\geq$3. Complications included severe abdominal pain, nausea/vomiting in all 7 cases, gastrointestinal paralysis in all 7 cases, circulatory disorders in all 7 cases, acute respiratory distress syndrome (ARDS) in 6 cases, liver dysfunction in 5 cases, and acute upper gastrointestinal bleeding in 4 cases. Three cases presented with ascites, and drainage was performed in these patients. Amylase levels in the drained ascitic fluid were $\geq$8,000 Somogyi units. We treated all 7 cases of HLAP with hemoperfusion (HP) in combination with continuous veno venous hemodiafiltration (CVVHDF). This combination satisfied therapeutic outcomes.

Treatment

Patients were required to fast after hospitalization. Gastrointestinal decompression, anti-shock treatment, inhibition of pancreatic secretion, antiseptic treatments, and a large dose of the Chinese medicine "Da Huang" to facilitate intestinal movement were administered to all the patients. The Chinese medicine, Danshen, and low molecular weight dextran were injected to improve microcirculation in the pancreas. Lipid-lowering medications were not administered during the early stage. After the treatments described, hemoperfusion in combination with hemodiafiltration (HP + CVVHDF) was administered: patients received HP + CVVHDF treatments each lasting 2–6 h (total duration of treatment 8–49 h) after hospitalization. The catheter was inserted through the jugular or femoral vein and connected to a Gambro AK 200 hemodialysis machine. A HA330-type macroporous resin plasma adsorption device (from Zhuhai Lizhu Medical Bio-material Co., Ltd., Zhuhai, China) was used as the filter. This product uses non-polar macroporous resin as the adsorbent and can effectively adsorb lipid-soluble macromolecules. Adsorption was performed for 2.0–2.5 h. Unfractionated heparin was then administered to prevent coagulation, with a primary single dose of 0.5 U/kg, followed by constant infusion using a pump at a rate of 10–15 U/h. If the TG level was $\geq$11.3 mmol/L, HA330 perfusion adsorption treatment was performed twice consecutively followed by CVVHDF treatment using the Gambro PrismaCRRT machine for 12.8 $\pm$ 10.4 h (total duration ranging from 4 to 36 h). The anticoagulant administered was selected based upon the patients' coagulatory function. The goal of using unfractionated heparin was to prolong the activated partial thromboplastin time (APTT) or activated clotting time (ACT) by at least 50 %.

Patient condition was constantly monitored in the ICU. Vital signs monitored included blood pressure, heart rate, breathing, blood gas levels, and arterial oxygen saturation (SaO_2); hemodynamic parameters monitored included arterial pressure, mean arterial pressure (MAP), and central venous pressure (CVP). Intra-abdominal pressure was also measured 4 times daily. Serum TG and total cholesterol (TC) were measured before and after treatment. Urine amylase, liver and kidney function, blood count, electrolyte levels, prothrombin activity, and evidence of any adverse reactions were checked daily. The rate of improvement was observed.

Statistical Methods

All statistical analyses were performed using the SPSS 12.0 software. The quantitative data were presented as a mean $\pm$ standard error. Data obtained before and after the treatment were compared using the *t* test. A p value <0.05 was considered significant.

Results

1. Laboratory test results for plasma TG, cholesterol, blood glucose, and serum and urine amylases, at the time of admission for each patient are shown in Table 1.

2. *Changes in lipid levels after HP treatment*: Serum TG and cholesterol levels were significantly decreased after treatment by resin adsorption ($p < 0.01$). TG levels decreased by 29.78 % and cholesterol levels by 24.02 % (Table 2).

3. *Changes in TG and total cholesterol after HP + CVVHDF combination treatment*: TG and TC levels dropped by 49.02 and 37.66 %, respectively, on day 1 post-treatment; by 62.81 and 47.37 % on day 2 post-treatment; and by 69.57 and 49.47 % on day 3 post-treatment (Table 3).

4. *Clinical outcomes and prognosis of sequelae after HP + CVVHDF combination treatment*: TG levels rapidly normalized within 48 h after administration of 1–3 rounds of HP + CVVHDF treatment. As lipid levels decreased, abdominal pain, nausea, and vomiting were relieved within

Table 1 The laboratory test results at admission of 7 patients

Number	Triglyceride (mmol/L)	Cholesterol (mmol/L)	Blood glucose (mmol/L)	Serum amylase (U/L)	Urine amylase (U/L)
1	20.8	11.8	18.1	580	1,970
2	12.7	6.5	15.3	774	2,013
3	14.4	7.8	14.0	320	3,109
4	16.3	8.5	19.9	810	3,254
5	8.5	6.9	13.2	680	5,410
6	11.6	6.1	12.9	480	3,980
7	12.1	7.9	16.0	508	2,790

Table 2 Changes in lipid levels after a single hemoperfusion ($x \pm s$)

Index (measurement)	Before perfusion	After perfusion	Change rate (%)	*t* Value	*P* value
TG (mmol/L)	13.77 ± 3.91	9.67 ± 2.31	29.78	3.84	≤0.01
TC (mmol/L)	7.93 ± 1.91	5.98 ± 1.32	24.59	4.11	≤0.01

TG triglyceride, *TC* total cholesterol

Table 3 Changes in lipid levels after HP + CVVHDF treatment (mean, mmol/L)

Index (measurement)	Before treatment	Day 1	Day 2	Day 3
TG (mmol/L)	13.77	7.02 (49.02 %)	5.12 (62.81 %)	4.19 (69.57 %)
TC (mmol/L)	7.62	4.75 (37.66 %)	4.01 (47.37 %)	3.85 (49.47 %)

24 h in all the patients and resolved within 48 h. Breathing and blood circulation returned to normal gradually. All the 7 patients survived the treatment, indicating in this study a 100 % survival rate. The average time spent in the ICU was 7 ± 3.8 days, and the average duration of hospitalization was 19 ± 15.1 days.

Discussion

From the results of this study, we were unable to draw any conclusions on the precise mechanisms of action underlying the etiology of HLAP. There are several commonly accepted mechanisms. It has been suggested that elevated lipid levels increase blood thickness, which impedes pancreatic microcirculation, and lead to HLAP. Blood viscosity could activate platelets, which will release the potent vessel constrictor Thromboxane A2 (TX-A2). The ratio of TX-A2 to the platelet inhibitory prostaglandin PGI2 will be disrupted, possibly contributing to the severity of pancreatitis. Another explanation could be lipid thrombi originating elsewhere in the body, which could dislodge and block pancreatic microcirculation. Serum lipid particles could aggregate, and these complexes could occlude the blood vessels supplying the pancreas. Alternatively, a large amount of free fatty acid (FFA) might be produced by the pancreatic lipase due to the increased hydrolysis of TG that could lead to FFA accumulation in the vicinity of and within the pancreas. These high levels of FFA would overwhelm the binding capacity of albumin, causing toxicity to the tissue and damaging the pancreatic acinar cells and the small vessels, ultimately causing AP.

The clinical course of HLAP is different from that of AP resulting from non-lipid related causes. It is strongly associated with early functional failure of other organs, late-stage pancreatic edema, and pancreatic pseudocyst formation. Kyriakidis et al.'s study shows that plasmapheresis successfully lowered lipid levels with no complications and relieved the patients from the symptoms in the acute phase of the disease [5]. Hence, the key to effective treatment is to reduce TG levels, and therefore systemic inflammation, in a swift manner. Blood cleansing therapies in China and other countries, which could be used to clear excess TG from the blood, include plasmapheresis, double membrane filtration, freezing lipid filtration, and immunoabsorptions. But the application of these therapies is restricted by the high cost, limited availability of plasma, and lack of quality control of blood products. Iskandar et al. reported that blood filtration not only allows for normalization of circulating inflammatory factors, but also enables absorption of TG [6] and removal of chylomicrons from circulation [3]. Our study has confirmed that blood filtration is an effective way to treat HLAP. The data presented here found that filtration can effectively inhibit inflammatory reactions in the early stage of severe HLAP (within 72 h after onset).

The polysulfone hollow fibers of the filtration device used in this study could potentially be blocked by TG, impairing the further removal of molecules of medium size from circulation. This problem was overcome by changing the filtration device multiple times during the course of treatment. The first-pass filtration serves largely the purpose of lipid absorption, and secondary filtration steps increase the removal of cytokines. Other studies, including the work done by Zhang's group [7], supported our findings. They found that blood TG, TC, and LDL were significantly reduced after resin perfusion and the reduction in TG levels was the most profound, which suggests that hemoperfusion could efficiently remove lipid from circulation. Jia [8] prescribed both hemoperfusion and hemodiafiltration to patients at early stages of severe HLAP and found that the TNF-α, IL-1, and IL-6 were all lowered by treatment; microcirculation was significantly improved; internal environment was stable, and all patients were given a positive prognosis. In our study, 7 patients with HLAP received a single hemoperfusion with resin, during which TG levels were significantly reduced. Hemodiafiltration therapy was administered following hemoperfusion, which led to a further rapid decrease in TG level. Following both treatments, patients reported that abdominal pain had quickly disappeared. Two days after hemodiafiltration, the overall condition of the patients was observed to ameliorate, with TG levels falling to >5.65 mmol/L. We can infer from our study data that hemoperfusion combined with hemodiafiltration is an efficient treatment that works more effectively than hemoperfusion alone. This combination therapy achieved profound reduction of the plasma lipid levels, improved the internal environment by removing inflammatory factors, and prevented the progression of HLAP early in the pathological process, leading to better prognosis.

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