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Use of Continuous Venovenous Hemodiafiltration with a High Cutoff Membrane in a Patient with Severe Acute Pancreatitis

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ABSTRACT

In patients with severe acute pancreatitis (SAP) early and persistent elevated circulating levels of interleukins (IL)-1, 2 and 6 and tumor necrosis factor (TNF)-α are linked to severity of disease and early multiple organ failure (MOF), while persistently elevated serum IL-10 is linked to immune paralysis and infectious complications. Although experimental and clinical evidence exists that continuous venovenous hemodiafiltration with high cutoff membranes (HCO-CVVHDF) efficiently removes inflammatory mediators from blood of patients with severe sepsis or septic shock, data are lacking on the subset of patients with SAP, particularly in cases with uninfected necrosis. We treated with HCO-CVVHDF a 59-year-old man admitted to our intensive care unit (ICU) with SAP inducing early-onset cardiovascular, respiratory and renal dysfunctions associated with high circulating levels of IL-6 and TNF-α and without overt clinical or laboratory signs of infection. During the treatment, cardiovascular, respiratory and renal functions rapidly normalized and circulating levels of IL-6 and TNF-α consistently decreased. The patient was discharged from ICU on day 20.

Keywords: Acute Pancreatitis; Multiple Organ Failure; Blood Purification

1. Introduction

Severe acute pancreatitis (SAP) is an acute systemic inflammatory disease with a poor prognosis in 7% - 15% of cases [1]. Early mortality is linked to multiple organ failure (MOF), which is led by extended pancreatic necrosis and systemic inflammatory damage to organs, typically lungs and kidneys [2]. In patients with SAP, the systemic inflammatory response is driven mostly by high circulating levels of IL-1, IL-6 and TNF-α. High levels of IL-6 are linked to severity of disease, early-onset multiple organ failure and increased mortality [2]. During the late phase of SAP, IL-10 may be predominant and lead to immune-paralysis and infectious complications, which are related to late-onset MOF and mortality [1]. We report our experience with a 59-year-old patient with SAP and early refractory MOF. Continuous venovenous hemodiafiltration with a high cutoff membrane (HCO-CVVHDF) effectively reversed severe on- going organ dysfunction.

2. Case Report

A previously healthy 59-year-old man (83 kg, 170 cm) sought treatment at our hospital after suffering abdominal pain associated with nausea for three days. Laboratory tests suggested acute pancreatitis (white blood cell count, WBCC = 1.29×10^4/L, serum amylase = 1248 U/L, total serum Ca^{++} = 6.0 mg/dl, procalcitonin (PCT) < 0.5 ng/ml). Variations over time of clinical and vital parameters are reported in **Table 1**. The first CT scan confirmed enlargement of the pancreas without necrosis and showed abdominal fluid collections along the posterior abdominal wall. Upon diagnosis of acute pancreatitis, continuous infusion of gabexate-mesilate 1000 mg/day was started. The next day the patient was confused and complained of breathlessness. Hypoxia was evident (pH 7.28, PaO_2 68 mmHg spontaneously breathing with FiO_2 50%, $PaCO_2$ 33 mmHg, BE-9.0, serum lactates 4.6 mmol/L). The trachea was intubated and mechanical ventilation started. He was subsequently transferred to our ICU. A new CT scan showed extended areas of pancreatic necrosis and fluid collections were evident around the gland, in the abdominal cavity and in the pleurae. On day 1, the patient was febrile (38.7˚C), tachycardic and hypotensive (see **Table 1**). Clinical management followed recommendations on SAP care [3,4]. Aggressive fluid therapy was started to achieve a central venous pressure of at least 8 mmHg [3]. A continuous infusion of noradrenaline was needed, at an initial dose of 0.25 g/kg/min, to maintain a mean arterial pressure (MAP) of 65 mmHg. Urine output decreased to 0.48 ml/kg/h and serum creati-

Table 1. Variations of clinical and laboratory parameters; the worst value is reported.

	Hospital admission	ICU-day 1	ICU-day 2 (prior initiation of CVVHDF)	ICU-day 4	ICU-day 6 (after withdraw of CVVHDF)
WBCC ($\times 10^3/\mu L$)	12.9	12.4	8.9	13.7	9.0
Body temperature (˚C)	35.8	38.7	37.5	35.7	36.4
PCT (ng/mL)	<0.5		1.2	0.7	0.7
PaO_2 (mmHg)	92	55	78	117	132
FiO_2 (%)	21	80	60	60	50
HI	438	68.75	130	195	264
Ventilation modality	-	BPAP (18/8)	BPAP (18/10)	ASB/CPAP (16/6)	ASB/CPAP (16/6)
Noradrenaline (g/Kg/min)	0	0.25	0.35	0	0
SOFA (points)	0	9	8	3	2

WBCC = white blood cell count; PCT = procalcitonin; HI = Horowitz Index (PaO_2/FiO_2); BPAP = Bilevel Positive Airway Pressure; ASB = Assisted Spontaneous Breathing; CPAP = Continuous Positive Airway Pressure.

nine rose from 0.66 to 1.43 mg/dl (RIFLE stage: Injury [5]). Intra-abdominal pressure (IAP) was 18 mmHg. SOFA score, APACHE-II score and Ranson score were 9, 16 and 4, respectively. Samples of blood, urine and bronchial secretions were taken for microbiological cultures, which turned out to be negative. Prophylaxis with piperacillin/tazobactam 4.5 g t.i.d. and fluconazole 800 mg/ daily was started. A naso-jejunal tube was inserted and enteral nutrition started. On day 2, the patient was worsening despite aggressive treatment. A high-dose noradrenaline infusion was still required to maintain a MAP of 65 mmHg. IAP was 22 mmHg, urinary output was 0.25 ml/Kg/h and serum creatinine 2.3 mg/dl. At this point serum TNF-*α*, IL-6 and IL-10 levels were 27 pg/ml (0 - 15 pg/mL), 422.7 pg/ml (0-10 pg/ml) and 10.7 pg/ml (0 - 15 pg/ml), respectively. HCO-CVVHDF (SeptexTM, Gambro-Hospal, Germany) was then started with the following settings: total blood flow, 180 ml/min; pre-dilution flow, 250 ml/h; dialysate flow, 2905 ml/h (35 ml/kg/ h); post-dilution flow, 250 ml/h; fluid removal was set as clinically appropriate.

Respiratory, cardiovascular and renal functions improved soon after initiation of HCO-CVVHDF (see **Table 1**). On ICU-day 4, blood gases were improved to the point that the patient was weaned from sedation and switched to assisted spontaneous breathing. He was not febrile, WBCC was 1.37×10^4/L and PCT was 0.7 ng/ml. IAP was 15 mmHg and urinary output rose up to 1.1 ml/ Kg/h. HCO-CVHHDF was suspended on day 6. At this point serum levels of TNF-*α*, IL-6 and IL-10 were 3.0 pg/ml, 49.3 pg/ml and 10.4 pg/ml, respectively. Hemodynamics and renal function continued to remain stable without further support. The patient failed two subsequent trials of spontaneous breathing and a percutaneous tracheostomy was done on ICU-day 9. The patient was completely weaned from MV on day 15. The last CT scan showed a regression of pancreatic inflammation and free fluid collections and the patient was discharged from ICU on day 20.

3. Discussion

In this case CVVHDF with a high cutoff hemofilter (*i.e.* with a pore size of about 0.01 μm) was effective in reversing a rapidly precipitating MOF syndrome due to SAP. HCO-CVVHDF was used as a "rescue" therapy and in the absence of clear clinical or laboratory signs of infection.

In patients with SAP, tissue necrosis leads to a systemic inflammatory response syndrome which is associated with early-onset organ failure. Immune-paralysis, increased infection susceptibility, increased gut permeability and bacterial translocation may be evident and are linked to infection of pancreatic necrosis and late-onset MOF [6]. Early high levels of IL-6 are related to disease severity and outcome, while elevated levels of IL-10 are related to immune-paralysis and infective complications [6-8], which are usually observed later. Cytokine-clearing blood purification techniques may therefore play a role in the treatment of patients with SAP [9-12]. A level of IL-6 > 400 pg/ml has been used by Abe *et al* [13] as an indication for starting "non-renal" CVVHDF with a cytokine-adsorbing membrane in a cohort of 90 patients with SAP. The Authors showed that mortality rate of treated patients was significantly lower than controls (6.1 vs. 25%), and this was associated with a reduction of IL-6 from 998 to 99 pg/mL (mean values). As pointed out by the those Authors, the reduction of blood levels of IL-6 is the key feature of their approach. High cutoff membrane hemofilters are particularly effective in clearing blood from inflammatory cytokines, with a sieving

coefficient for IL-6 which is higher than standard membranes [14]. Thus, those membranes could be particularly useful to treat patients with SAP. Consistently, in this case clinical improvement was associated with a tenfold reduction in serum levels of IL-6, which fell from 422.7 pg/mL to 49.3 pg/mL (0 - 10.0 pg/mL); similarly, TNF-α decreased from 27 to 3 pg/ml. On the contrary, IL-10 was not high, as expected in early severe acute pancreatictis.

As previously observed in our experience, arterial pressure improved rapidly after initiation of HCO-CVVHDF and, despite the high blood flow and total effluent dose, noradrenaline infusion was interrupted after only 14 hours of treatment (see **Table 1**). This is consistent with SAP pathophysiology and observations made by other Authors [1,2]. Renal function and respiratory func- tion improved rapidly during the treatment (see **Table 1**); unfortunately, respiratory weaning was slow and a tracheostomy was needed for prolonged ventilatory support. This may be due to the patient's physical habitus and the extension of pancreatic necrosis, which led to persistently high intra-abdominal pressure.

In this case, clear clinical evidence of infection was lacking. However, since inflammatory mediators play a role in pathogenesis of both septic and non-septic systemic inflammatory response syndromes, HCO-CVVHDF may be useful in either sterile or infected SAP. Moreover, there is evidence that cytokine removal can improve gut barrier function in patients with SAP [15], which could potentially prevent bacterial translocation, bacteremia and infection of necrotic tissues. There is also evidence that HCO-CVVHDF may restore native immunity competence and T-lymphocyte function, thus improving antibacterial immunity and contributing to prevent infective complications and late mortality [12].

With these membranes, CVVHDF with low flows of replacement fluid is preferable to pure hemofiltration because of the risk of significant protein loss with high-volume convection, which could increase the retroperitoneal edema and the intra-abdominal pressure. The "high flux" dose we employed is in line with actual recommendations [14].

Some points need to be outlined. First, most of the clinical evidence for these techniques is extrapolated from studies in patients with abdominal sepsis [16]. Clinical benefit in patients with SAP has been shown, until now, only in small numbers of patients and only with high-volume continuous venovenous hemofiltration or heamoadsorption [17]. While the use of anti TNF-alpha antibodies to blunt inflammatory response was not effective in improving survival rates in septic patients [18-20], blood purification techniques could be beneficial since they can reduce the concentration of many inflammatory mediators at the same time, thus modulating inflammatory and anti-inflammatory response [9].

Second, the clinical benefit of renal replacement therapies in SAP patients may be due to effects other than the mere clearing of cytokines. Fluid removal may reduce retroperitoneal edema, thus contributing to improved absorption of enteral nutrition, reduced bacterial translocation and, possibly, a reduced rate of infective complications. Active fluid removal decreases intra-abdominal pressure, improves lung compliance and ventilation and improves splanchnic circulation, contributing to preserve or restore renal function. Despite those considerations, our case shows that use of HCO-CVVHDF can be considered at an early stage for patients with SAP and MOF, as part of a complex therapeutic approach, and that in selected cases it may be useful in limiting mortality of those patients, which is high. However clinically appropriate and useful, these techniques should be considered alongside other recommended clinical interventions [4].

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