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Hemoperfusion plus continuous veno-venous hemofiltration in the treatment of patients with multiple organ failure after wasp stings

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Abstract

Purpose: This study aimed to evaluate the clinical effects of hemoperfusion plus continuous veno-venous hemofiltration in the treatment of patients with multiple organ failure after wasp stings and investigate its impacts on cytokines.

Methods: A total of 12 patients with multiple organ failure after wasp stings admitted to Xijing Hospital were included in the present study between January 2017 and January 2019. All patients received hemoperfusion plus continuous veno-venous hemofiltration treatment in addition to conventional treatment after admission. Procedure of treatment was conducted as the following: hemoperfusion (2 h/day) and followed by continuous veno-venous hemofiltration (22 h/day) for at least 5 days. Patients' clinical features, serum laboratory tests, and hemodynamic variables were monitored. The blood samples were taken to measure the changes of plasma cytokines.

Results: All 12 patients survived in the observation period. After hemoperfusion plus continuous veno-venous hemofiltration treatment, there were significant improvements in indicators of liver function, renal function, state of consciousness, and mediators in blood circulation, including alanine transaminase, aspartate transaminase, creatine kinase, blood urea nitrogen, serum creatinine, myoglobin, C-reactive protein, and so on. In these patients, acid–base metabolism returned to normal levels; Acute Physiology and Chronic Health Evaluation II score, Simplified Acute Physiology Score II score, and Sequential Organ Failure Assessment score lowered markedly. Furthermore, the plasma levels of interleukin 1β, interleukin 4, interleukin 6, interleukin 8, and interleukin 10 in these patients were significantly decreased; no significant change was shown in the level of tumor necrosis factor α.

Conclusion: Our results revealed that hemoperfusion plus continuous veno-venous hemofiltration was effective in the management of patients with multiple organ failure after wasp sting via the non-specific removal of the wasp venom and inflammatory cytokines.

Keywords

Hemoperfusion, continuous veno-venous hemofiltration, multiple organ failure, wasp sting, cytokine

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Introduction

Wasp stings are a common form of envenomation in developing countries, especially in rural areas.[1–3] There are many reports about complications after wasp stings. However, severe life-threatening multiple organ failure (MOF) after wasp stings is rarely documented. The wasp venom contains several active substances, including melittin with hemolytic and vasoactive properties, histamine, hyaluronidase, apamin, phospholipase A_2, and acid phosphatase.[4] In fact, in addition to acute renal failure (ARF), hepatocyte damage, intravascular hemolysis, rhabdomyolysis, thrombocytopenia, coagulopathy, cardiovascular, and neurological abnormalities are the severe complications caused by wasp venom.[1–7] Furthermore, inflammatory reaction activated by wasp venom was another difficult problem to be dealt with. The wasp venom can induce the excessive release of pro-/anti-inflammatory mediators, such as tumor necrosis factor (TNF-α), interleukin-1 (IL-1), IL-6, and IL-8.[8] Some studies showed that about 500 stings may lead to death by the direct toxicity of wasp venom, but as few as 30 stings can also cause fatal systemic envenomation.[9] And it is reported that high concentrations of wasp venom could be detected after 50 h of wasp stings which indicated its continuous damages to body.[1] It is critical to antagonize the toxic effects of wasp venom and remove the circulating mediators of inflammation as soon as possible.

In the past, conventional therapy including glucocorticoid, anti-inflammatory agents, fluid therapy, nutritional supports, and other essential organ supportive therapies were applied to treat patients with MOF stung by wasps. However, no specific and safe therapy is currently available for the effective treatment of MOF resulting from mass wasp attacks; these measures mentioned above seemed not to be able to protect the function of vital organs of patients and restore the homeostasis in patients. Our previous findings suggest that continuous blood purification (CBP) exerts beneficial effects on the clinical course in critically ill patients and is effective in removal of many plasma cytokines from patients.[10,11] Considering there are many toxins and inflammatory mediators in the blood circulation of patients with wasp stings, single blood purification modality may not be effective in clearance of them, hybrid CBP modality is often recommended. The aim of this retrospective study was to evaluate the clinical effects of hemoperfusion (HP) plus continuous veno-venous hemofiltration (CVVH) in the treatment of patients with MOF after wasp stings and investigate its impacts on cytokines.

Materials and methods

Patients

A total of 12 patients with MOF after wasp stings admitted to Xijing Hospital were included in the present study between January 2017 and January 2019. Diagnosis was made according to the criteria for MOF, including confirmed wasp stings, and the occurrence of dysfunction or failure of two or more organs successively or simultaneously 24 h after the wasp stings. The patients included nine males and three females, ranged from 8.4 to 65.1 years old. All patients received HP plus CVVH treatment in addition to conventional treatment after admission. Conventional treatment included wound debridement, giving glucocorticoid, anti-inflammatory agents, fluid therapy, pain-palliative therapy, nutritional supports, and other essential organ supportive therapies. When necessary, positive end-expiratory pressure, inspiratory oxygen supply, and inotropic support were applied. The study protocol was approved by the local ethics committee and conducted according to the principles established at Helsinki. Informant consent was obtained from all patients or their relatives.

Procedures of HP and CVVH

For HP plus CVVH treatment, a double lumen catheter was inserted into the internal jugular of patients to establish vascular access. Procedure of treatment was conducted as the following: HP (2 h/day) and followed by consecutive CVVH (22 h/day) for at least 5 days and prolonged when necessary. The HP was performed using a neutral macroporous resin (HA330, Zhuhai Lizhu Medical Bio-Material Co., Ltd., China). For CVVH, the bicarbonate substitution fluid was infused at a rate of 35 mL/kg per hour in a pre-diluted manner (before the hemofilter) and the blood flow rate ranged 150–250 mL/min. An AV1000S hemofilter (Fresenius, Bad Homburg, Germany) was used in adult patients and AV 400S hemofilter was used in adolescent patients. To prevent clotting, low-molecular weight heparin (Fraxiparine, 0.2–0.4 mL) was given at the start of treatment. Then, Fraxiparine was infused into the blood circuit every 4 h to maintain an activated clotting time (ACT) of 160–180 s. For patients with a tendency to bleed (activated partial prothrombin time (PT) >120 s), we used an in vitro anticoagulant instead of heparin. Net fluid removal was set according to the patient's condition and clinical need.

Data collection and measurement

Level of consciousness, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR), respiratory, renal, hematologic, and coagulation variables were monitored in all patients. Appropriate laboratory and physiological variables were recorded for calculation of the Acute Physiology and Chronic Health Evaluation (APACHE) II score, Simplified Acute Physiology Score (SAPS), and Sequential Organ Failure Assessment (SOFA). And blood samples were taken at the beginning and the end

of treatment for measurement. Plasma was obtained after centrifugation (at 3000*g*, 10 min, 4°C) and stored at −70°C until further analysis. All biochemical parameters were measured by standard auto-analyzers in the laboratory department at the Xijing Hospital. Concentrations of TNF-α, IL-1β, IL-4, IL-6, IL-8, and IL-10 in serum were measured using a commercially available enzyme-linked immunosorbent assay kit (R&D Systems, Minneapolis, MN, United States). Each cytokine sample was run in duplicate, and the mean cytokine concentration was calculated.

Statistical analysis

Descriptive data were analyzed for all variables. Quantitative data were expressed as the mean values ± standard deviation (SD), and student's *t*-test and Mann–Whitney rank tests were employed to evaluate the difference between groups. The *P* values reported were two-sided, and a *P* value <0.05 was considered statistically significant. All the analyses were performed using SPSS software (version 22.0, SPSS Inc., United States).

Results

Clinical features and complications of patients with MOF after wasp stings

A total of 12 patients with MOF after wasp stings were enrolled in this study. These patients included nine males and three females, ranged from 8.4 to 65.1 years old. Among these patients, acute kidney injury (AKI) was seen in all 12 cases, acute liver dysfunction in 8 cases, metabolic acidosis in 6 cases, coagulation disorder and fever in 5 cases, pulmonary infection in 4 cases, coma, hypotension, hyperkalemia, and myocardial damage in 2 cases, and congestive heart failure in 1 case (data were shown in Table 1). All of patients were suffering from two or more complications.

Table 1. Clinical features and complications of patients with MOF after wasp stings.

Symptoms and complications	*n*	%
Acute kidney injury	12	100
Acute liver dysfunction	8	66.7
Metabolic acidosis	6	50.0
Coagulation disorder	5	41.7
Fever	5	41.7
Pulmonary infection	4	33.3
Coma	2	25.0
Hypotension	2	16.7
Hyperkalemia	2	16.7
Myocardial damage	2	16.7
Congestive heart failure	1	8.3

MOF: multiple organ failure.

Effects of HP plus CVVH treatment on laboratory parameters of patients with MOF after wasp stings

With the treatment of HP plus CVVH, there were significant improvements in the parameters of liver and kidney functions in these patients. The levels of alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin index (TBI), indirect bilirubin index (IBI), lactate dehydrogenase (LDH), blood urea nitrogen (BUN), and serum creatinine (SCr) dropped markedly. The indicators of pH, HCO_3^-, and base excess returned to the normal range which meant that metabolic acidosis were corrected. In addition, the levels of white blood cells, creatine kinase-MB (CK-MB), C-reactive protein (CRP), and myoglobin decreased after treatment. On the contrary, the levels of hemoglobin, platelet count, and albumin rose, respectively. The data were shown in Table 2.

Effects of HP plus CVVH treatment on physiological and hemodynamic variables of patients with MOF after wasp stings

After HP plus CVVH treatment, the severity of illness in these patients improved. APACHE II score, SAPS II score, and SOFA score decreased significantly, while SBP, DBP, MAP, and PaO_2/FiO_2 increased. Furthermore, the comatose patients regained responsiveness to painful stimuli, eye-opening, and lingual ability after treatment, and Glasgow score rose from 9.8 ± 2.1 to 12.9 ± 1.7. The data were shown in Table 3.

Changes of plasma cytokines before and after HP plus CVVH treatment

With the treatment of HP plus CVVH, the levels of IL-1β, IL-4, IL-6, IL-8, and IL-10 dropped from 12.4 ± 2.8, 128.6 ± 24.4, 175.9 ± 38.6, 93.3 ± 18.1, and 57.5 ± 16.3 to 4.7 ± 0.6, 36.9 ± 10.2, 113.5 ± 12.7, 33.4 ± 8.8, and 41.2 ± 9.1, respectively. But there is no significant change in the level of TNF-α before and after HP plus CVVH treatment. The data were shown in Figure 1.

Clinical outcomes of patients with MOF after wasp stings

With respect to clinical outcomes, all of 12 patients survived in the observation period. On day 6, one patient was transferred to the local hospital for treatment. The duration of oliguria and hospitalization of the remaining patients were 9.4 ± 3.2 and 12.5 ± 2.9 days, respectively. One patient required additional temporary intermittent

Table 2. Effects of HP plus CVVH treatment on laboratory variables of patients with multiple organ failure after wasp stings.

Variables	Pre-treatment	Post-treatment	*P*
ALT (IU/L)	747.6 ± 447.5	112.3 ± 36.9	<0.0001
AST (IU/L)	812.7 ± 538.2	124.8 ± 49.5	<0.0001
Albumin (g/L)	28.3 ± 6.8	32.6 ± 7.2	0.147
TBI (μmol/L)	81.9 ± 17.3	41.8 ± 14.4	<0.0001
IBI (μmol/L)	59.2 ± 21.7	22.9 ± 12.6	<0.0001
BUN (mmol/L)	23.3 ± 10.6	11.8 ± 7.7	0.006
SCr (μmol/L)	453.7 ± 121.2	127.5 ± 41.3	<0.0001
pH	7.31 ± 0.04	7.42 ± 0.03	<0.0001
HCO_3^- (mmol/L)	18.4 ± 4.3	25.1 ± 1.8	0.0075
BE (mmol/L)	−5.5 ± 1.4	2.1 ± 0.2	<0.0001
HB (g/dL)	7.9 ± 1.5	9.6 ± 1.7	0.0164
WBC (10^9/L)	15.6 ± 3.9	12.1 ± 2.6	0.0168
Platelet count (10^9/L)	69.7 ± 18.3	152.4 ± 34.5	<0.0001
LDH (U/L)	5349.6 ± 1123.7	856.4 ± 179.4	<0.0001
CK-MB (U/L)	1312.3 ± 434.5	456.6 ± 137.8	<0.0001
CRP (mg/L)	32.2 ± 9.3	12.3 ± 5.7	<0.0001
Myoglobin (ng/mL)	1357.5 ± 321.1	438.9 ± 98.5	<0.0001

HP: hemoperfusion; CVVH: continuous veno-venous hemofiltration; ALT: alanine transaminase; AST: aspartate transaminase; TBI: total bilirubin index; IBI: indirect bilirubin index; BUN: blood urea nitrogen; SCr: serum creatinine; BE: base excess; HB: hemoglobin; WBC: white blood cells; LDH: lactate dehydrogenase; CK-MB: creatine kinase-MB; CRP: C-reactive protein.
Data are expressed as mean values ± SD.

Table 3. Effects of HP plus CVVH treatment on hemodynamic and physiological variables of patients with MOF after wasp stings.

Variables	Pre-treatment	Post-treatment	*P*
SBP (mmHg)	112.4 ± 18.7	135.2 ± 15.9	0.0040
DBP (mmHg)	67.1 ± 12.6	83.7 ± 9.2	0.0013
MAP (mmHg)	82.4 ± 15.9	101.5 ± 11.8	0.0030
HR (beats/min)	112.6 ± 17.3	91.3 ± 15.5	0.0044
PaO_2/FiO_2 (mmHg)	292.4 ± 121.7	413.6 ± 54.2	0.0046
APACHE II score	21.6 ± 6.7	13.7 ± 4.1	0.0021
SAPS II score	42.9 ± 15.2	24.8 ± 9.3	0.0019
SOFA score	14.5 ± 4.6	6.3 ± 2.8	<0.0001
Glasgow score	9.8 ± 2.1	12.9 ± 1.7	0.0006

HP: hemoperfusion; CVVH: continuous veno-venous hemofiltration; MOF: multiple organ failure; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; HR: heart rate; PaO_2/FiO_2: the ratio of arterial oxygen partial pressure to fractional inspired oxygen; APACHE: Acute Physiology and Chronic Health Evaluation score; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment.
Data are expressed as mean values ± SD.

hemodialysis (IHD) after discharge and recovered completely later. All the laboratory parameters turned to normal levels, and no complications were observed in these patients at day 90.

Discussion

In the present retrospective study, the clinical effects of HP plus CVVH in patients with MOF after wasp stings were observed, and its impacts on cytokines were evaluated. Considering the illness severity and clinical efficacy, no patients without receiving CBP were compared as control. Our results demonstrated that after wasp sting, these patients were all suffering from two or more complications and excessive production of plasma cytokines was seen in these patients. After HP plus CVVH treatment, there were significant improvements in the laboratory parameters and the severity of illness in these patients. Furthermore, the plasma levels of IL-1β, IL-4, IL-6, IL-8, and IL-10 in these patients were markedly decreased.

Patients with MOF after wasp stings are associated with a high mortality rate. The MOF after wasp sting is due to direct toxicity or inflammatory reaction activated by wasp venom. The direct toxic effects of wasp venom may induce a local reaction or trigger immediate hypersensitivity.

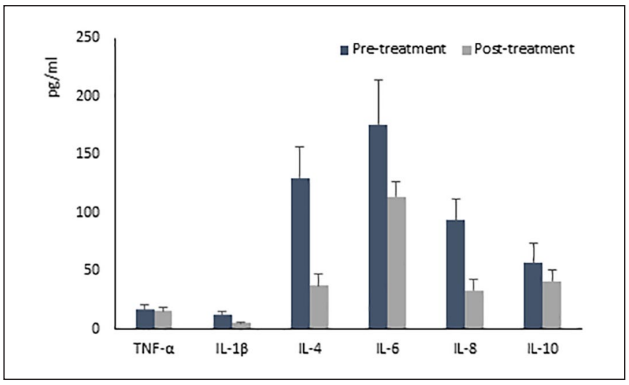

Figure 1. Changes of plasma cytokines before and after HP plus CVVH treatment.

However, when a person received multiple stings, a severe toxic reaction mimicking anaphylaxis usually developed and followed by a delayed-type reaction mediated by T lymphocytes and excessive release of cytokines.[12] In addition to specific signs and symptoms directly related to the venom toxic components, patients bitten by wasps may develop a systemic inflammatory response syndrome.[4,8,9] There is also evidence of acute-phase reaction with hyperthermia or hypothermia, leukocytosis, neutrophilia, lymphopenia, eosinophilia, some clotting disorders, and protein imbalance with the increase in CRP and decrease in total proteins.[13,14] Increasing evidence from animal studies and clinical experience showed that the involvement of the inflammatory cascade and release of cytokines play a major role in the pathogenesis of wasp stings. Cytokines are a diverse group of proteins of relatively low-molecular weight with multiple functions.[15–17] Pro-inflammatory cytokines such as TNF-α and IL-1β can induce local and systemic inflammatory manifestations. The local effects include the activation of vascular endothelium, increase in vascular permeability, and access of leukocytes into the affected tissue and their activation and local tissue destruction. The systemic manifestations include fever, the acute-phase response, and induction of a systemic shock in severe inflammatory processes.[15–19] Anti-inflammatory cytokines such as IL-4 and IL-10 also appear to play a significant role in modulating acute inflammation and allergic reactions. They can down-regulate the effects of pro-inflammatory cytokines, release of PGE_2, and up-regulate the expression of IL-1.[15,17,19,20] In our study, patients were all suffering from two or more complications which might be induced by the excessive production of plasma cytokines. It is critical to take measures to antagonize the effects of wasp venom, remove the excessive release of inflammatory cytokines, and restore the balance of immune homeostasis in the patients with MOF after wasp sting as soon as possible.

In recent years, blood purification technology has been widely used in many fields of clinical practice.[10,11,21–23] Blood purification technology include many different modalities, such as IHD, HP, CVVH, continuous veno-venous hemodiafiltration (CVVHDF), plasma exchange (PE), and so on. HP is effective in removal of mid- to large-sized molecules and toxins bound to proteins, and it is widely used to manage cases of drug overdose and intoxications.[21,24] Moreover, HP has a therapeutic role in systemic inflammatory response syndrome, acute respiratory distress syndrome, sepsis, acute necrotic pancreatitis, and wasp venom-induced AKI.[21,24–26] The resin HP apparatus used in our study is HA 330, which is reported to be effective in the removal of macromolecular-weight inflammation mediators and endotoxins.[27,28] CVVH is an extracorporeal technique that provides CBP treatment based on three mechanisms: diffusion, convection, and adsorption; convection and adsorption are the principal ways to remove mid- to large-sized molecules. In addition to removing excess fluid and sodium, it was reported that the excessive inflammatory response could be alleviated with CVVH by non-specific clearance of cytokines and other mediators.[10,11,29–31] In our study, improvements on hemodynamic variables, clinical outcome, and down-regulation of cytokines were significant after HP plus CVVH treatment. The efficacy of CVVH to remove cytokines varied greatly among many findings.[32–34] Some studies indicated that the levels of plasma cytokines were not lowered after CVVH treatment. But in these studies, cytokines were detected in ultrafiltration liquids after CVVH therapy which indicated that cytokines were really removed from blood.[34] The difference in severity of disease, the timing, hemofiltration volume, modality, and the filter of CVVH used in these studies may contribute to the different results. In the present study, the plasma levels of IL-1β, IL-4, IL-6, IL-8, and IL-10 were markedly decreased after HP plus CVVH treatment, while there is no significant change in the level of TNF-α. It is reported that for cytokines with small molecular weight, CVVH clearance ability is superior to those with large molecular weight or polymer. The smaller the molecular weight is, the better the clearing ability of CVVH. The molecular weight of IL-1β, IL-4, IL-6, IL-8, and IL-10 is comparatively smaller than TNF-α; so, perhaps it is the main reason why their removal is superior to TNF-α.[14–19,32–34]

In conclusion, our results revealed that HP plus CVVH was effective in the management of patients with MOF after wasp sting. But some limitations of this study should be considered. Our study is a retrospective, single-center study with very small sample size. Considering the illness severity and clinical efficacy, no patients without receiving CBP were compared as control. And we only measured the levels of cytokines in serum; the levels of these cytokines in the effluence were not measured. In future, more large-scale, multi-center controlled clinical trials are still needed to validate the effects and mechanisms of HP plus CVVH treatment further.

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