

Clinical effectiveness of continuous blood purification in combination with ulinastatin in treating thermoplegia

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Abstract. – OBJECTIVE: To explore the clinical effectiveness of continuous blood purification (CBP) in combination with ulinastatin for the treatment of thermoplegia.

PATIENTS AND METHODS: Forty patients (28 men and 12 women) with severe heat stroke were admitted to our hospital's ICU department from June 2010 to August 2013. The patients were randomized into a treatment group (n=21; 15 men and six women, with an average age of 32.9 years) and control group (n=19; 13 men and six women, with an average age of 33.1 years). Patients in the control group underwent treatments of oxygen inhalation, dynamic ECG monitoring, physical cooling methods (ice caps or ice application), whereas patients in the treatment group, in addition to this treatment, were further treated with continuous blood purification in combination with ulinastatin. During administration, the content of one vial was dissolved in 100 mL of physiological saline for intravenous dripping for 1.5 hours.

RESULTS: There were 18 cured cases, one case of sequelae of mild neurological disorders, and two deaths in the treatment group, with the cure rate of 90.48%. In comparison, there were 12 cured cases, three cases of sequelae of mild neurological disorders, and four deaths in the control group, with the cure rate of 78.95%. The overall response rates of rectal temperature drop were determined to be 95.24% and 73.68% for the treatment group and the control group, respectively. Based on the treatment outcomes data, multiple organ dysfunction syndrome (MODS) recovery, deaths and survival outcomes of patients in the treatment group was more favorable than that of the control group. This difference was statistically significant ($p < 0.05$).

CONCLUSIONS: Continuous blood purification in combination with ulinastatin is effective in treating thermoplegia and warrants further investigation.

Key Words:

Continuous blood purification, Ulinastatin, Heat stroke, Treatment.

Introduction

Heat stroke is characterized by the dysfunction of thermoregulation, sweat gland failure, excessive loss of water and electrolytes, as a result of exposure to heat, humidity, and wind-free environments. Depending on the pathogenesis and clinical manifestations, severe forms of heat stroke could be divided into heat cramps, heat exhaustion, and thermoplegia. These conditions might develop sequentially amongst which thermoplegia is the most severe form. Thermoplegia is characterized by the dysfunction of the nervous system and malignant hyperthermia (acute elevation of body temperature of more than 40 °C), systemic inflammatory reactions, coagulation, liver dysfunction and other multi-organ dysfunction. The mortality rate of heat stroke is as high as 40-50%, with approximately 30% of the surviving patients recovering with sequelae to the nervous system or other systems¹. Lowering body temperature and a regimen against complications are the key to a successful treatment of heat stroke. Favorable outcomes were observed in the treatment of heat stroke by continuous blood purification (CBP) in combination with ulinastatin, as described as follows.

Patients and Methods

Clinical data

Forty patients with severe heat stroke were admitted to our hospital's ICU department from June 2010 to August 2013. There were 28 males and 12 females, aging from 22 to 65 years old, with an average age of 32.98 years. All patients had environmental heat exposure within one hour of disease onset, with the body temperature at more than 40°C at admission. The timeframe between disease onset and emergency visit was 0.5-6 hours. Findings on physical examination include HR of 92-156 bpm,

breath rate of 30-46 times per minute, and blood purification (BP) of 5-183/52-120mmHg. Clinical manifestations include facial flushing or pallor, skin burning sensation, high temperature, excessive sweating, cramped breath, rapid pulse rate, little urination, disturbance of consciousness, abdominal or limb spasms. All these subjects were randomized into the treatment group (21 subjects) and a control group (19 subjects). There were 15 males and six females in the treatment group, with an average age of 32.9 years. For the control group, there were 13 males and six females, with an average age of 33.1 years. There were no statistically significant intergroup differences in age, gender, prior medical history, and conditions at admission ($p > 0.05$). Cardiovascular and cerebrovascular accident, CNS infection, typhoid, epilepsy and toxic diseases were excluded in all patients.

Treatment

After admission, patients in the control group underwent comprehensive treatments of oxygen inhalation, dynamic ECG monitoring, and physical cooling methods (ice caps or ice application). Prevention and treatment of shock, cerebral edema, respiratory, liver, renal, and heart failures, disseminated intravascular coagulation (DIC), and water and electrolyte imbalance were also performed. Patients in the treatment group received CBP in combination with ulinastatin in addition to the regimen prescribed for patients in the control group. Ulinastatin (Techpool Bio-Pharma Co., Ltd, Guangdong, 100,000 units per vial; Batch No: 03070223) tid was administered. During administration, the content of one vial was dissolved in 100 mL of physiological saline for intravenous dripping for 1.5 hours. This therapy lasted for one week. For CBP, vascular access was established by direct catheterization of femoral vein or the internal jugular vein using an ABLE disposable double-lumen hemodialysis catheter. The method of continuous venovenous hemodiafiltration (CVVHDF) was used in CBP. Baxter CT190 and HF1200 Hemodiafilters were used; the replacement fluid of bicarbonate formulation recommended by the Nanjing General Hospital was applied, with the input and output rates of 3.5-5.0 L/h for the replacement fluid, the blood flow rate of 200-250 ml/min and the ultrafiltration flow rate of 200-350 ml/h. The first dose of unfractionated heparin was 0.6-1.0 mg/kg, with up-titration of 5-10 mg per 0.5-1.0 h. APTT was monitored. In the session of CBP, BP, ECG, oxygen saturation, and body temperature were monitored. Post-dose co-

agulation function, electrolytes, blood gas analysis, and hepatic and renal function were monitored. This therapy lasted for one week.

Outcome measures

Therapeutic efficacy against hyperthermia was judged as follows: complete response: rectal temperature dropped to the normal range; partial response: rectal temperature dropped to below 39°C with low or moderate hyperthermia; no response: no downward trend of body temperature, remained still above 39°C. Therapeutic efficacy against consciousness disorders was judged as follows: complete response: recovered to clear awareness; partial response: disturbance of consciousness reduced to drowsiness; no response: no improvement in disturbance of consciousness. The recovery time of multi-organ dysfunction, fatalities and average survival were examined in both two groups.

Statistical Analysis

The *t*-test and chi-square test was implemented based on the SPSS14.0 platform software package (SPSS Inc., Chicago, IL, USA). $p < 0.05$ was considered statistically significant.

Results

Drop Profile of Rectal Temperature of Patients with Heat Stroke

In the treatment group, it took 3.76 ± 0.46 hours on average to achieve the therapeutic target of a complete rectal temperature drop, and 21.76 ± 3.95 hours on average to achieve the therapeutic target of a partial rectal temperature drop. In the control group, it took 6.83 ± 0.95 hours on average to achieve the therapeutic target of a rectal temperature drop for patients with a complete response, and 36.51 ± 5.89 hours on average for patients with a partial response. Based on the results in the hypothermic response and the timeframe to achieve a rectal temperature of 36 °C between these two groups, the rectal temperature drop was more helpful in the treatment group than in the control group ($p < 0.05$) (Table I).

Improvement Profile of Consciousness Disorders

In the treatment group, it took 3.15 ± 0.98 days on average to achieve the therapeutic target of complete consciousness recovery, and 6.75 ± 3.17 days on average to achieve the therapeutic target of partial consciousness recovery. In the control group, it

Table I. Drop profile of rectal temperature between these two groups

Group	n	Complete response (n)	Partial response (n)	No response (n)	Overall response rate (%)
Treatment group	21	9	11	1*	95.24*
Control group	19	7	7	5	73.68

* $p < 0.05$, compared with control group.

took 6.92 ± 1.21 days on average to achieve the therapeutic target of complete consciousness recovery, and 18.66 ± 5.53 days on average to achieve the therapeutic target of partial consciousness recovery. Based on the results of statistical analyses, there was a statistically significant difference in the cure rate between these two groups ($p < 0.05$), as detailed in Table II.

Recovery of MODS, Fatality and Survival

It took 5.25 ± 1.98 days on average to achieve the recovery of MODS for the treatment group, and 9.89 ± 3.03 days for the control group. There were two deaths in the treatment group and four deaths in the control group. The average survival of patients was 21.06 ± 3.98 days in the treatment group, and 32.96 ± 6.95 days in the control group. More favorable outcome was observed in the treatment group compared to the control group. The difference was statistically significant ($p < 0.05$).

Based on the data described in Tables I-II, there were 18 treated cases, a case of sequelae of mild neurological disorders, and two deaths in the treatment group, with the cure rate of 90.48%, according to consciousness improvement and cooling effect. In comparison, there were 12 treated cases, three cases of sequelae of mild neurological disorders, and four deaths in the control group, with the cure rate of 78.95%. The overall response rates of rectal temperature drop were determined to be 95.24% and 73.68% for the treatment and the control group, respectively. Based on the data of consciousness improvement, cooling effect, MODS recovery, deaths and survival, the treatment outcome

of patients in the treatment group was more favorable than that of the control group. This difference was statistically significant ($p < 0.05$).

Discussion

Known as the most severe heat stroke, thermoplegia is considered to be induced by internal or external thermal load exceeding the corresponding heat dissipation capacity, leading to overheating as a result of excessive body heat storage. Excessive heat accumulation might damage the cell membrane and intracellular structures of human tissues and was associated with protein thermal denaturation, fluidity changes in lipid membrane, resulting in mitochondria injury and extensive damages of tissues and cells, and then MODS. Since thermoplegia bears similar pathogenesis in many aspects with sepsis. There are many studies available to investigate the value of anti-sepsis agents in the treatment of thermoplegia. The roles of reduction of inflammatory cytokines (such as IL-6) and elevation of anti-inflammatory cytokines (e.g. IL-10) secretion have been demonstrated in the treatment of thermoplegia². In terms of heat stroke-induced nervous system injury, the administration of dexamethasone and mannitol in combination was associated with significant prolongation of survival and reduced nervous system damage in rats with thermoplegia³. Supplementation of hyperbaric oxygen could also alleviate the nervous system damage of mouse with thermoplegia⁴. Moreover, the combination of hyperbaric oxygen and activated protein C

Table II. Improvement profile of consciousness disorders between these two groups

Group	n	Complete response (n)	Partial response (n)	No response (n)	Overall response rate (%)
Treatment group	21	13	6	2*	90.46*
Control group	19	8	7	4	78.95

* $p < 0.05$, compared with control group.

is associated with significant survival prolongation of rats with thermoplegia⁵. As demonstrated by recent studies, infection, trauma, and fever could induce early inflammatory reactions and release of inflammatory mediators, considered to be an important step to develop systemic inflammatory response syndrome (SIRS), compensatory anti-inflammatory response syndrome (CARS) and MODS. Moreover, early anti-inflammatory intervention, blockage of its progression or effective removal of circulating inflammatory mediators might be the key to the prevention and treatment of SIRS, CARS, and MODS.

Since SIRS plays a role in the pathogenesis of thermoplegia, anti-inflammatory agents, such as glucocorticoids⁶, Ulinastatin⁷, could be used to block relevant inflammatory responses, in addition to CBP which could be used to remove inflammatory mediators. As one of the typical K-unit protease inhibitors, Ulinastatin has dual functions and could suppress the activities of hydrolytic enzymes responsible for protein, carbohydrate and lipid. This agent can inhibit the activities of the hydrolytic enzymes of various proteins, carbohydrates, and lipids and the creatine phosphokinase and has a stabilizing effect on the lysosomal membrane; thus, can be used to protect the functions of multiple vital organs.

For the treatment of thermoplegia, early rapid cooling strategy is the most important therapeutic intervention, with the goal rectal temperature of 38.5°C within two hours, maintained in the range of 34.5-35.5°C within four hours, to achieve favorable prognosis^{8,9}. The endovascular cooling strategy is the latest cooling concept, and continuous bedside blood filtering method could reduce a patient's temperature, with a remarkable efficacy¹⁰. Continuous blood purification is a newly developed BP technology based on intermittent hemodialysis and had multi-target therapeutic effects as follows: a) effective temperature-lowering performance; b) effective removal of myoglobin, bilirubin, and other toxic substances; and c) non-selective removal of inflammatory mediators in the blood, reduction of systemic inflammatory response, contributing to the reconstruction of homeostasis.

Conclusions

In this study, the use of CBP and ulinastatin in the treatment of thermoplegia was associated with favorable cooling performance, removal of inflammatory mediators and blockage of inflammatory response. A

total of 21 patients with thermoplegia underwent CBP and ulinastatin therapy. Considering the aspects of an improvement in consciousness, cooling effect, MODS recovery, and deaths and survival, more favorable outcomes were observed in the treatment group than in the control group. No adverse reaction was reported. The recommended regimen to treat the most severe form of heat stroke (thermoplegia), is a combination of CBP and ulinastatin.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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