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Therapy of Severe Heatshock in Combination With Multiple Organ Dysfunction With Continuous Renal Replacement Therapy

A Clinical Study

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Abstract: This study aimed to compare the clinical effects of continuous renal replacement therapy (CRRT) and routine therapy in heatshock (HS) patients.

We retrospectively reviewed the clinical information of 33 severe exertional HS patients who were treated from February 1998 to October 2013. On the basis of whether or not CRRT therapy was used in addition to conventional therapy, patients were divided into a CRRT group (n = 15) and a control group (n = 18). Body temperature, blood gas analysis, routine blood tests, blood eletrolytes, enzymes and kidney function data, and APACHE II scores were obtained and compared between the 2 groups on admission and 3, 5, and 7 days after admission. Mortality was also compared between the 2 groups.

CRRT treatment combined with conventional treatment resulted in a higher hospital-discharge rate, a faster return to normal of body temperature, greater increase in platelets, a greater decrease in WBC, neutrophils, and serum markers for liver and kidney dysfunction, greater improvement of organ dysfunction, and lower APACHE II scores than conventional treatment used alone.

The addition of CRRT to conventional treatment for HS improves survival and causes a faster return to normal of serum markers and organ function.

Editor: Francois Vincent.
Received: December 25, 2014; revised: June 18, 2015; accepted: June 28, 2015.
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This study was funded by the research subject of the 11th Five-Year Plan of Nanjing military region.
The authors have no conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000001212

(*Medicine* 94(31):e1212)

Abbreviations: BMI = body mass index, CRRT = continuous renal replacement therapy, DBP = diastolic blood pressure, DIC = disseminated intravascular coagulation, HR = heart rate, HS = heatshock, MAP = mean arterial pressure, MODS = multiple organ dysfunction, PAR = pressure-adjusted heart rate, RR = respiratory rate, SBP = systolic blood pressure.

INTRODUCTION

Heatshock (HS) is a clinical syndrome caused by central thermoregulatory dysfunction. Patients with severe HS may develop extensive tissue injury, neurological dysfunction, rhabdomyolysis, disseminated intravascular coagulation (DIC), and multiple organ dysfunction (MODS).[1,2] Nonexertional HS is caused by long-term exposure to high environmental temperature. Exertional HS is caused by strenuous exercise under conditions of high environmental temperature and humidity. HS is a critical illness with rapid progression and high mortality. Mortality can be as high as 62.6% in heatstroke not induced by exercise, even in the presence of appropriate and timely therapy.[3]

Cooling by immersion in ice water has been shown to be the most rapid method of reducing core temperature,[4] and current therapy for HS is rapid cooling combined with supportive therapy for organ dysfunction. However, one of the most important mediators of heatshock toxicity is the systemic inflammatory response that occurs.[1] A therapy that removes inflammatory mediators and other heat-shock invoked toxic substances should improve recovery from this condition.

Continuous renal replacement therapy (CRRT) can reduce the inflammatory response, clear toxic metabolites, rectify water, electrolyte, and acid/base imbalance, and maintain homeostasis.[5] Although studied extensively for the treatment of sepsis,[6,7] its potential usefulness in HS therapy has not been thoroughly investigated. In the current study, we retrospectively reviewed clinical information of 33 patients with severe exertional HS, and compared the effect of CRRT (using continuous veno-venous hemofiltration) combined with routine treatment to the effect of routine treatment alone on the following potential indicators of recovery: temperature reduction, survival, blood gas analysis, routine blood tests including blood electrolytes, enzymes and indicators of kidney function, and APACHE II score on admission and 3, 5, and 7 days after admission.

METHODS

Patients

Records of 33 patients with severe HS treated in our hospital from February 1998 to October 2013 and their clinical information were reviewed. This retrospective study was approved by Fuzhou General Hospital of Nanjing Military Command, PLA. Patient records/information was anonymized and deidentified before analysis. Written informed consent was given by participants for their clinical records to be used in this study.

On the basis of whether or not CRRT was added to conventional HS treatment, patients were divided into CRRT (15 patients) and control (18 patients) groups. All patients were diagnosed with severe HS[8] and had hyperthermia (body temperature: 39.6–42.0 °C), disturbance of consciousness, dizziness, low blood pressure, abnormal liver function, acute kidney injury, and rhabdomyolysis. Diagnostic criteria[9] for MODS were met in all patients. To be assigned to the CRRT group, both patient and family member agreed to CRRT therapy, were able to meet the cost of this therapy, and had a physician who agreed to provide this therapy. The control group were patients who, like the CRRT group, met the conditions of HS accompanied by MODS but had only routine treatment. CRRT therapy was not introduced until 2004, so the earliest CRRT patient was from 2004, while the earliest control patient was from 1998.

The following data were abstracted from the patient records: body temperature, blood gas information, routine blood test results, blood electrolytes, enzymes, kidney function, APACHE II score, recovery of organ function, and mortality.

Treatments

Routine Therapy

All patients were given antibiotics. According to the patient's clinical condition, physical cooling, sedation, liquid supplementation, anti-inflammatory treatment, anti-shock measures, liver protection, rectification of water and electrolyte imbalance, and support therapy were performed. Physical cooling was done with an ice water bath and/or an alcohol sponge bath. Supportive therapy was done with mechanical ventilation, an ice cap for brain cooling, neurotrophic agents, and measures to reduce intracranial pressure. Platelets were infused when platelet levels were $<5 \times 10^9$, with a bleeding tendency.

CRRT Therapy

Routine therapy was performed in all CRRT patients. CRRT was added to this therapy 3 to 25 hours after admission. Femoral vein or subclavian vein catheterization was performed for blood access. Blood flow rate was 180–200 mL/min, and replacement fluid rate was 2500–4000 mL/hour.

Fresh replacement fluid was prepared before each procedure. The volume of replacement fluid used was not constant in all patients but was adjusted according to individual patient requirements. The predilution method was used to prepare the fluid so that the anti-coagulation dosage requirement was lower, and coagulation was less likely to occur in the filtration equipment, and at the same time increasing safety. The electrolyte concentration ranges used were the following: Na^+, 135–150 mmol/L; Cl^-, 95–116 mmol/L; HCO_3^-, 30–35 mmol/L; Ca^{++}, 1.8–2.1 mmol/L; Mg^{++}, 1.5–1.7 mmol/L; glucose, 8.7–12.14 mmol/L; K^+, 2.5–4.2 mmol/L. Calcium gluconate was added at a uniform rate according to the replacement fluid rate. Replacement fluid components were adjusted according to blood water, electrolyte, and acid/base findings of each patient. Either, heparin, low molecular weight heparin, or no-haprin was used provided depending on the patient's coagulation function. Replacement fluid was given at room temperature (about 20–25 °C). Six patients in the CRRT group also received plasmapheresis due to acute liver failure (once in 4 patients and twice in 2 patients). At each plasmapheresis session, 2000–2500 mL of plasma was replaced within 2.5 hours.

An ADM-08 (Fresenius, Germany), BM-25 continuous bedside blood purification machine (Baxter, USA), an AV-600S polysulfone membrane filter (Fresenius, Germany), P_2S plasma separator (Fresenius, Germany), and 11.5Fr double lumen hemodialysis catheters (Arrow, USA) were used for CRRT.

Comparison of Outcome Data

Comparisons between CRRT and conventional treatment were made for time course of body temperature reduction, mortality, blood gas analysis, routine blood tests, and blood electrolytes, enzymes and kidney function, and APACHE II score on admission and 3, 5, and 7 days after admission. In determining the APACHE II score, the worst value was collected for each item. An item not filled in was scored 0, and the presence of 2 items not filled in was defined as incomplete data. Patients with incomplete data were not scored.

Recovery and improvement of organ function were also compared between groups. Recovery was defined as absence of clinical symptoms and return to normal serological parameters. Improvement was defined as the improvement of clinical symptoms, but serological parameters not returning to normal. For central nervous dysfunction, improvement was defined as improved clinical manifestations and Glasgow score >12, and recovery as absence of clinical manifestations and Glasgow score of 15. For cardiovascular dysfunction, improvement was defined as improved clinical manifestations and pressure-adjusted heart rate (PAR) $<$ 20 ($PAR = HR \times CVP/MAP$), and recovery as absence of clinical manifestations and PAR <10. For respiratory dysfunction, improvement was defined as improved clinical manifestations and PaO_2/FiO_2 >225 mm Hg, and recovery as absence of clinical manifestations and O_2/FiO_2 >300 mm Hg. For liver dysfunction, improvement was defined as improved clinical manifestations and bilirubin <7 mg/dL, and recovery as absence of clinical manifestations and bilirubin <1.2 mg/dL. For kidney dysfunction, improvement was defined as improved clinical manifestations and creatinine <4 mg/dL, and recovery as absence of clinical manifestations and creatinine <1.1 mg/dL. For coagulation dysfunction, improvement was defined as improved clinical manifestations and platelet count $>80 \times 10^9$/L, and recovery as absence of clinical manifestations and platelet count $>120 \times 10^9$/L. For gastrointestinal dysfunction (abnormal or absent *bowel* sounds, retention of food in the stomach or a positive occult blood feces test with dark stools or haematermesis, abdominal distension), improvement was defined as alleviation, and recovery as disappearance of the above manifestations.

Statistical Analysis

Continuous data are presented as mean ± standard deviation (SD), and categorical data as numbers and percentages. Comparisons for baseline characteristics between control and CRRT treatment were performed by independent t-test for

continuous data, and χ^2 or Fisher exact test for categorical data. Due to the repeated measurements of clinical parameters across time, a linear model with generalized estimating equations (GEE) was applied to investigate the effect of CRRT treatment (denoted as Group), time after admission (denoted as Time), and their interaction (denoted as Group × Time). When main effects or interactions showed significance, further post-hoc multiple comparisons were conducted by Bonferroni correction to adjust over-all type I error rates. Regarding survival-to-discharge, the survival curves were constructed by the Kaplan–Meier method with a log-rank test to detect the difference between control and CRRT treatment. The 30-day mortality was estimated by the Kaplan–Meier method with 95% confidence interval. Statistical analyses were performed with SAS software version 9.2 (SAS Institute Inc, Cary, NC). A two-tailed $P < 0.05$ indicated statistical significance.

RESULTS

Baseline Characteristics of HS Patients with Control and CRRT Treatment

Thirty-three patients were included in this study; baseline characteristics are summarized in Table 1. The average duration from HS to admission for the control and CRRT groups was 12.9 ± 3.6 and 12.5 ± 3.5 hours, respectively ($P = 0.703$). CRRT therapy was given to patients at an average time of 7.9 hours after admission and 20.4 hours after HS. Two in the CRRT group and 1 in the control group had hypertension with regular medication. The baseline distribution for age, sex, BMI, body temperature, HR, RR, SBP, DBP, and MAP did not differ between the 2 groups (all $P > 0.05$).

At admission, 3 patients in the CRRT group required mechanical ventilation, and the durations were 89, 98, and 168 hours, respectively. The patients requiring 168 hours was not successfully weaned from ventilation. At admission, 4 patients in the control group required mechanical ventilation, and the durations were 168, 216, 240, and 312 hours, respectively. None of these 4 patients were successfully weaned, and all subsequently died. In addition, 7 patients in the control group were intubated and mechanically ventilated before death, the duration ranged from 19–78 hours.

Both groups received volume expansion, and vasopressor medications (eg, dopamine, dobutamine, etc.) in the early hours of HS, but no detailed records were kept of these interventions. However, we observed a trend that for the CRRT group, that after CRRT, the requirement for vasopressors was gradually reduced or terminated, but for the control group, the dosage of vasopressors required was greater and the medication duration was longer.

Body Temperature During the 72 hours After Admission

Body temperature decreased during the 72 hours after admission in both control and CRRT treatment groups (Figure 1). The decrease in body temperature was significantly greater ($P = 0.049$), and the time taken for body temperature to return to normal (37 °C) was significantly shorter in the CRRT group than the control group (11.9 ± 6.8 vs. 29.2 ± 11.3 hours; $P < 0.001$).

Organ Dysfunction

Better improvement and recovery from organ dysfunction was seen in the CRRT than in the conventional treatment group

TABLE 1. Baseline Characteristics of Patients with Heat Stroke Compared Between Control and CRRT Treatment

	Control (n = 18)	CRRT (n = 15)	*P* Value
Age, yr			0.607†
Mean ± SD	28.4 ± 11.6	30.9 ± 15.1	
Range	19.0–61.0	16.0–64.0	
Sex, n (%)			1.000‡
Male	16 (88.9)	13 (86.7)	
Female	2 (11.1)	2 (13.3)	
BMI, kg/m^2			0.851†
Mean ± SD	23.8 ± 3.9	23.6 ± 3.3	
Range	17.7–30.5	18.3–30.1	
Body temperature, °C			0.407†
Mean ± SD	40.6 ± 0.7	40.4 ± 0.7	
Range	39.6–42.0	39.2–41.9	
HR, beats/min			0.820†
Mean ± SD	125.0 ± 20.5	126.7 ± 21.1	
Range	85.0–169.0	98.0–164.0	
RR, breaths/min			0.925†
Mean ± SD	29.4 ± 7.3	29.7 ± 9.5	
Range	18.0–45.0	17.0–47.0	
SBP, mm Hg			0.393†
Mean ± SD	99.7 ± 20.8	92.9 ± 23.9	
Range	50.0–148.0	38.0–136.0	
DBP, mm Hg			0.458†
Mean ± SD	57.7 ± 15.5	53.6 ± 15.4	
Range	30.0–90.0	24.0–75.0	
MAP, mm Hg			0.416†
Mean ± SD	71.7 ± 16.8	66.7 ± 17.6	
Range	36.7–109.3	28.7–87.7	
Duration from HS to admission, hr			0.703†
Mean ± SD	12.9 ± 3.6	12.5 ± 3.5	
Range	8.0–21.0	8.0–21.0	
Duration from admission to CRRT, hr			NA
Mean ± SD	NA	7.9 ± 7.1	
Range	NA	3.0–25.0	
Duration from HS to CRRT, hr			NA
Mean ± SD	NA	20.4 ± 9.6	
Range	NA	12.0–46.0	
Length of hospital stay, days			0.873†
Mean ± SD	22.7 ± 11.7	22.0 ± 12.0	
Range	7.0–42.0	7.0–41.0	
Body temperature at start of CRRT, °C			NA
Mean ± SD	NA	39.4 ± 1.1	
Range	NA	37.4–40.6	
Duration of CRRT treatment, hr			NA
Mean ± SD	NA	101.4 ± 42.1	
Range	NA	24–164	
Time until temperature decrease to 37 °C			<0.001*,†
Mean ± SD	29.2 ± 11.3	11.9 ± 6.8	
Range	(12–48)	(5–28)	

BMI = body mass index; CRRT = continuous renal replacement therapy; DBP = diastolic blood pressure; HR = heart rate; MAP = mean mean arterial pressure; NA = nonavailable; RR = respiratory rate; SBP = systolic blood pressure; SD = standard deviation.

* $P < 0.05$ indicates significantly different between groups.

† Determined by independent t-test.

‡ Determined by Fisher exact test.

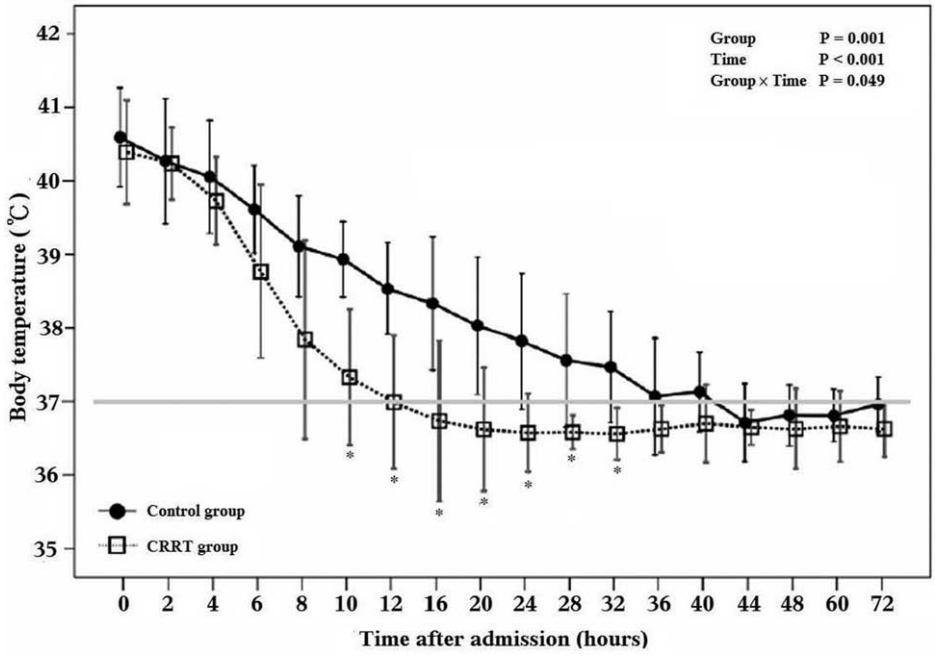

FIGURE 1. The trends of body temperature of patients with heat stroke compared between control and CRRT treatment across time. The error-bar (mean ± SD) of each group was located at time points of 0, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 60, and 72 hours after admission, respectively. A slight separation was made for error-bars among groups within the same time point to avoid overlapping. Significance found with post-hoc test using Bonferroni correction: * compared to control group, $P < 0.05$. CRRT = continuous renal replacement therapy; SD = standard deviation.

(Table 2). The proportion of patients with 4 or more organ dysfunctions at admission was not significantly different in the 2 groups. But after treatment, the patients who underwent CRRT therapy had better recovery of heart ($P = 0.005$), liver ($P = 0.029$), blood ($P = 0.003$), and gastrointestinal system ($P = 0.048$) function than those with conventional therapy.

WBC, Neutrophils, and Platelets

After treatment, the CRRT group had decreased WBC and neutrophils, and elevated platelets compared with the control group (Figure 2). At the end of the study (Day 7), the WBC (8.1 ± 0.2 vs. $12.1 \pm 4.8 \times 10^9$; $P = 0.049$) and neutrophils (64.1 ± 14.5 vs. $75.9 \pm 10.9\%$; $P = 0.039$) were significantly lower, and platelets were significantly higher (172.8 ± 72.7 vs. $90.8 \pm 59.1 \times 10^{12}$; $P = 0.002$) in CRRT than in control patients.

Electrolytes

Although there was no significant difference between groups in electrolyte concentrations on Day 5; on this day, 1 patient developed hyponatremia and 3 patients had hypernatremia in the control group. No hypo- or hypernatremia was seen in the CRRT group on Day 5. Also, although electrolyte imbalance was observed in several patients in the CRRT group, the incidence and severity of electrolyte imbalance in the CRRT group was lower than in the control group (Supplemental Table 1, http://links.lww.com/MD/A343).

On Day 7 (Table 3), the CRRT group had significantly higher Ca^{++} concentrations than those in the control group (2.3 ± 0.1 vs. 2.1 ± 0.3 mmol/L; $P = 0.049$). Na^+, K^+, and Cl^- concentrations in the 2 groups were similar at all time points.

Blood Gas Analysis

After treatment, patients in the CRRT group had less acidosis than the control group, that is, increased pH and HCO_3, decreased $PaCO_2$, and a smaller anion gap (Table 3). On Day 7, the $PaCO_2$ (39.2 ± 7.6 vs. 47.4 ± 7.6 mm Hg; $P = 0.012$) and anion gap (3.0 ± 4.1 vs. 20.1 ± 6.5 mmol/L; $P = 0.004$) were significantly lower, and pH (7.4 ± 0.1 vs. 7.2 ± 0.1; $P = 0.015$) and HCO_3 (20.8 ± 4.2 vs. 14.7 ± 6.0 mmol/L; $P = 0.009$) were significantly higher in the CRRT than in the control group.

TABLE 2. Organ Dysfunction of Patients with Heat Stroke Compared Between Control and CRRT Treatment

	Control (n = 18)	CRRT (n = 15)	*P* Value
Patients with organ dysfunction, n (%)			0.741*
3 organs or less	7 (38.9)	5 (33.3)	
4 organs or more	11 (61.1)	10 (66.7)	
Specific organ status (total no./cured no./improved no.)			
Brain	6/1/0	5/3/1	0.242†
Heart	13/3/0	13/11/0	0.005†
Lung	4/0/0	3/2/0	0.143†
Liver	15/1/5	13/6/5	0.029†
Kidney	15/4/1	9/6/1	0.092†
Blood	11/2/0	12/10/0	0.003†
Gastrointestinal	5/0/0	4/3/0	0.048†

CRRT = continuous renal replacement therapy.
* Determined by χ^2 test.
† Determined by Fisher exact test.

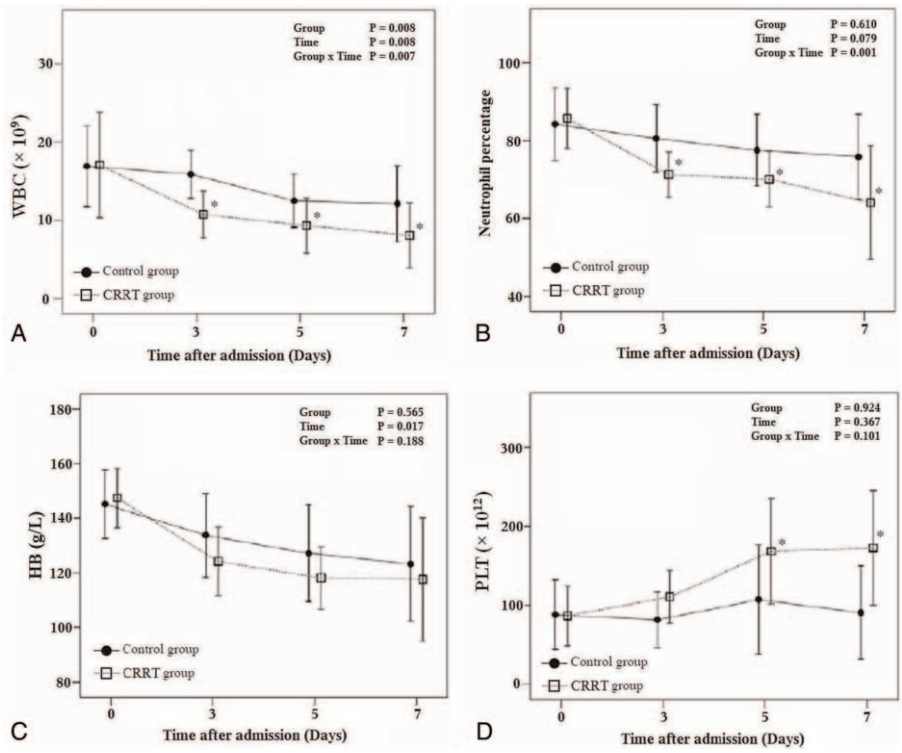

FIGURE 2. The trends of blood routine examination of patients with heat stroke compared between control and CRRT treatment across time: (A) white blood cells (WBC), (B) neutrophil percentage, (C) hemoglobin (HB), (D) platelets (PLT). The error-bar (mean ± SD) of each group was located at time points of 0, 3, 5, and 7 days after admission, respectively. A slight separation was made for error-bars among groups within the same time point to avoid overlapping. Significance found with post-hoc test using Bonferroni correction: *compared to control group, $P < 0.05$. CRRT = continuous renal replacement therapy; SD = standard deviation.

Serum Enzymes and Other Biomarkers

After treatment, levels of serum biomarkers for liver and kidney dysfunction were significantly reduced in CRRT, compared with conventionally treated patients (Table 3). On Day 7, the CRRT group had significantly reduced levels of CK (369 ± 359 vs. 1386 ± 1223 U/L; $P = 0.011$), LDH (404 ± 355 vs. 912 ± 701 U/L; $P = 0.037$), ALT (183 ± 173 vs. 624 ± 657 U/L; $P = 0.04$), AST (112 ± 113 vs. 605 ± 653 U/L; $P = 0.018$), Cr (114 ± 64 vs. 320 ± 221 μmol/L; $P = 0.004$), and BUN (7.2 ± 3.3 vs.14.8 ± 8.8 mmol/L; $P = 0009$) compared with the control group.

APACHE II Scores and Mortality

On day 7, the CRRT group had significantly lower APACHE II scores than those with conventional therapy (10.9 ± 6.3 vs. 18.2 ± 8.8; $P = 0.045$, Figure 3).

Two patients in the CRRT group and 11 patients in the control group died before discharge. Those 2 patients in CRRT and the 8 patients in control group died within 30 days before discharge in addition. The 30-day mortality was 15.2% (95% CI: 4.0–48.8%) and 45.5% (95% CI: 25.8–70.8%) for CRRT and control groups, respectively. There was no significant difference between CRRT and control groups in the 30-days survival before discharge ($P > 0.05$; results not shown). However, there were 3 patients died 30 days after discharge in CRRT group. Kaplan–Meier survival curves indicated that patients with CRRT therapy had better hospital-discharge for overall compared with those with conventional therapy (Figure 4) ($P = 0.029$).

Adverse Events

One of the 13 patients who received CRRT within 24 hours developed cardiac arrest but recovered after resuscitation. This patient, a female aged 16, experienced severe HS during a mountain hike. She was admitted to another hospital, where cardiac arrest and resuscitation occurred. After resuscitation (9-hour postinitial HS), the patient was transferred to our hospital where, at initial hospitalization, she was unconscious, had a body temperature of 40°, multiple organ dysfunction, and DIC. Four hours after admission to our hospital (13 hours postinitial HS), CRRT treatment was started. Seven hours after CRRT initiation, her body temperature was lowered to 37°. The total CRRT treatment was 16 hours. The patient survived with recovery of all organs, but with adverse neuro-sequellae (compromised IQ, and some physical dysfunction). However, after physiotherapy, the patient was able to perform basic daily routines by herself.

The 2 patients who received CRRT more than 24 hours (39.5 and 46 hours) after HS both died. Unlike the other CRRT patients, their temperature was already close to normal when CRRT was initiated, but because multiple organ function was already present, CRRT was performed. Of these patients, 1 patient, aged 64 years, had a history of hypertension, diabetes, coronary heart disease, and cerebral infarction. Both had

TABLE 3. Trends of Blood Gas Analysis, Electrolytes, Serum Enzymes and Other Biomarkers of Patients with Heat Stroke Compared Between Control and CRRT Treatment Across Time

		Measurements* Across Time Points				p-values from GEE analysis		
Paramenters	**Group**	**0 day**	**3 days**	**5 days**	**7 days**	**group**	**time**	**group × time**
Blood gas analysis								
pH	Control	7.32 ± 0.1	7.18 ± 0.17	7.2 ± 0.16	7.22 ± 0.15	0.739	0.049	0.003
	CRRT	7.3 ± 0.11	7.39 ± 0.03∗	7.35 ± 0.09∗	7.36 ± 0.09∗			
PaCO2, mm Hg	Control	37.95 ± 7.59	39.88 ± 5.7	44.58 ± 6.57	47.4 ± 7.58	0.303	0.038	0.432
	CRRT	35.47 ± 6.44	35.99 ± 3.54	38.14 ± 5.08∗	39.18 ± 7.59∗			
HCO3, mmol/L	Control	15.84 ± 2.69	13.99 ± 4.96	15.02 ± 5.78	14.73 ± 5.96	0.975	0.347	0.001
	CRRT	15.88 ± 3.73	21.57 ± 2.38∗	20.35 ± 4.09∗	20.77 ± 4.18∗			
AG, mmol/L	Control	13.77 ± 3.96	19.08 ± 5.77	19.21 ± 6.59	20.08 ± 6.45	0.731	0.014	<0.001
	CRRT	14.28 ± 4.66	9.07 ± 3.01∗	12.88 ± 3.3∗	13.02 ± 4.09∗			
Electrolytes								
Sodium (Na), mmol/L	Control	144.28 ± 13.84	147.53 ± 12.89	141.25 ± 4.8	137.38 ± 7.75	0.335	0.051	0.002
	CRRT	148.73 ± 13.08	141 ± 5.1	139.31 ± 2.63	138.28 ± 2.55			
Potassium (K), mmol/L	Control	4.77 ± 1.57	5.23 ± 1.48	4.81 ± 0.87	4.51 ± 0.9	0.631	0.148	0.018
	CRRT	5.03 ± 1.69	4.45 ± 0.76	4.34 ± 0.36	4.27 ± 0.44			
Chlorine (Cl), mmol/L	Control	103.17 ± 8.21	105.6 ± 6.96	104.56 ± 5.15	99.75 ± 7.2	0.434	0.037	0.122
	CRRT	105.33 ± 8	104.38 ± 3.86	103.77 ± 2.89	100.31 ± 4.4			
Calcium (Ca), mmol/L	Control	2 ± 0.31	1.89 ± 0.27	2.08 ± 0.24	2.09 ± 0.32	0.794	0.039	0.048
	CRRT	1.97 ± 0.33	2.11 ± 0.12	2.2 ± 0.13	2.3 ± 0.13			
Serum enzymes and other biomarkers								
CK, U/L	Control	3315.33 ± 2401.65	4038.2 ± 3018.54	2007.94 ± 1504.88	1386.13 ± 1222.72	0.913	0.021	0.007
	CRRT	3408.53 ± 2605.81	1386.38 ± 478.18∗	746.62 ± 311.08∗	369.43 ± 359.25∗			
LDH, U/L	Control	1290.06 ± 823.09	1248.53 ± 749.85	1010.38 ± 616.51	912.19 ± 701.28	0.065	0.018	0.023
	CRRT	1137.13 ± 905.71	757.77 ± 653.69	479.31 ± 417.46∗	404.08 ± 354.6∗			
ALT, U/L	Control	808.11 ± 929.39	1076.07 ± 954.86	758.88 ± 739.38	623.69 ± 657.21	0.993	0.039	0.046
	CRRT	811.08 ± 927.29	541.54 ± 418.48	304.08 ± 297.38	183.17 ± 173.14∗			
AST, U/L	Control	913.17 ± 1014.11	1029.87 ± 965.48	773.19 ± 728.09	605.19 ± 652.66	0.984	0.054	0.056
	CRRT	919.87 ± 939.97	543.31 ± 492.53	256.46 ± 203.6∗	112.38 ± 113.06∗			
BUN, mmol/L	Control	18.25 ± 11.33	19.77 ± 9.07	17.69 ± 9.61	14.79 ± 8.8	0.777	0.052	0.002
	CRRT	19.28 ± 10.19	12.01 ± 4.92∗	9.08 ± 3.54∗	7.18 ± 3.35∗			

CRRT = continuous renal replacement therapy; SD = standard deviation. Significance found with post-hoc test using Bonferroni correction: ∗compared to control group, $P < 0.05$.

* Data were represented as mean ± SD.

developed MODS due to long-term (>24 hours) exposure to high environmental temperature. Although blood gas and electrolytes returned to normal after CRRT, HS progressed continuously, serum enzymes and bilirubin continuously increased, platelet and fibrinogen levels progressively decreased, and coagulation dysfunction gradually increased. These 2 patients died of respiratory failure, liver failure, and DIC at 54 hours and 6 days after CRRT. In the CRRT group, 5 patients developed concomitant DIC, and of the 3 in whom early CRRT was done, all survived after therapy. In the routine therapy group, 4 patients with DIC died and another patient died of respiratory and circulatory failure.

DISCUSSION

Patients treated with CRRT in the current study had a significantly higher survival-to-discharge rate than patients who received conventional treatment only. This higher survival was accompanied by a faster return to normal of body temperature, a greater correction of acidosis, decrease in WBCs and neutrophils, and increase in platelets, and lower APACHE II scores than were achieved by conventional treatment alone. They also had decreased serum levels of biomarkers for liver and kidney dysfunction, and more extensive improvement of and recovery from organ dysfunction.

Rapid cooling and organ support have been effective strategies for the therapy of HS, but mortality is high. In 1 study, HS mortality within 28 days after a heat wave was as high as 58%.[10] Another study reported that reducing body temperature to 38.9 °C within 1 hours after HS may significantly reduce mortality.[11] In CRRT, the temperature, amount, and rate of replacement fluid can be adjusted in a way that helps to reduce core temperature. In the present study, body temperature returned to normal in a significantly shorter time in the CRRT group. This was probably due to the fact that the replacement fluid was given at room temperature, rather than body temperature.

In the present study, all HS patients were diagnosed with MODS: nervous system disorders in 22 patients, acute respiratory distress syndrome in 7, acute liver failure in 6, acute kidney injury in 18, DIC in 9, and rhabdomyolysis in 22. Routine therapy for HS with MODS is often done via symptomatic treatment and organ support. Supplementation with albumin and use of diuretic agents are treatments for reducing intracranial pressure. Expansion of the blood volume to increase

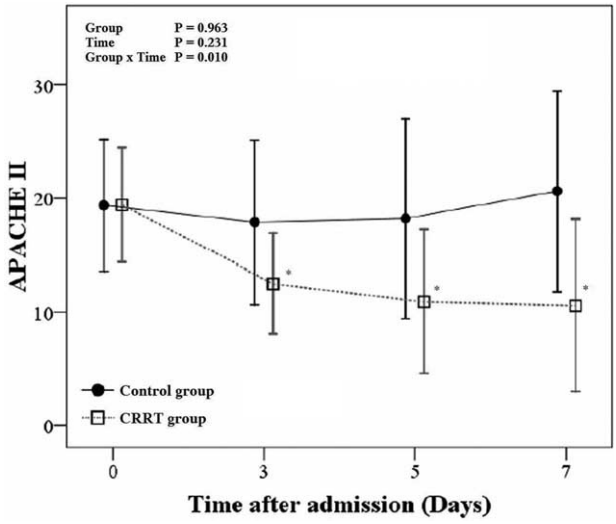

FIGURE 3. The trends of APACHE II score of patients with heat stroke compared between control and CRRT treatment across time. The error-bar (mean ± SD) of each group was located at time points of 0, 3, 5, and 7 days after admission, respectively. A slight separation was made for error-bars among groups within the same time point to avoid overlapping. Significance found with post-hoc test using Bonferroni correction: *compared to control group, $P < 0.05$. CRRT = continuous renal replacement therapy; SD = standard deviation.

urine volume and attenuate myoglobin-induced damage to the renal tubules is a treatment for rhabdomyolysis. Liquid supplementation is required to treat loss of body fluid and disturbances of water and electrolytes and acid/base imbalance. However, liquid supplementation may cause further aggravation of edema, and heavy liquid supplementation is not recommended for patients with concomitant heart failure and/or lung edema. Thus, there are conflicts in the conventional therapy of HS combined with MODS.

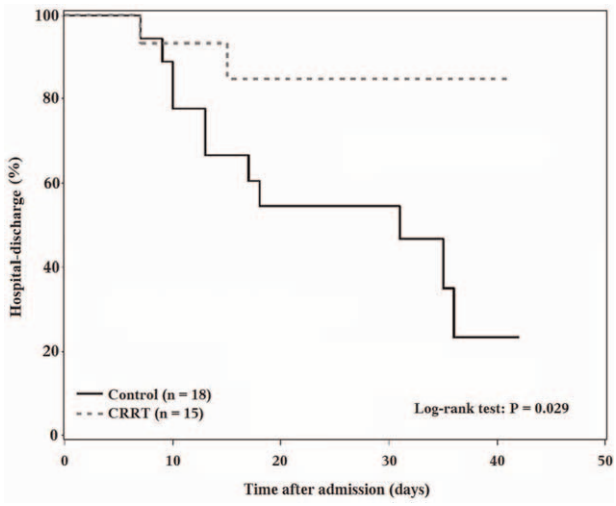

FIGURE 4. Kaplan–Meier estimators of hospital-discharge for patients with heat stroke compared between control and CRRT treatment. CRRT = continuous renal replacement therapy.

CRRT plays an irreplaceable role in the treatment of critical illness,[1] and can clear inflammatory mediators and metabolic products, rectify water and electrolyte disturbances, and improve acid/base balance. In addition, in the presence of heavy liquid supplementation, accurate ultrafiltration is helpful to attenuate organ edema and heart overload. In 2 studies, one in which severe heatshock was induced in dogs[12] and another in which 16 HS patients were treated with CRRT,[13] improved hemodynamics and serum enzyme concentrations were reported and no deaths occurred. In the present study, no significant differences in the Cr, BUN, ALT, AST, and CK were seen on admission, but before discharge, these HS-related parameters were significantly reduced in the CRRT compared with the control group. These data suggest that CRRT will clear serum enzymes and metabolic products, block the cascade of inflammatory mediators, and attenuate metabolite-induced damage to the renal tubules. In our study mortality was significantly lower in the CRRT group ($P < 0.05$). Thus, we should consider early CRRT therapy for HS patients because HS has high mortality once it enters the late stage (ie, with DIC).

This study has a number of limitations. Its power was limited because of the small number of patients. MODS or Sequential Organ Failure Analysis scores were not available. The study was monocentric and retrospective. The inclusion period spanned a long time period and changes in treatment during this period might have biased the results. However, no significant changes in routine clinical treatment of HS treatment occurred at our institution during the years of the study, and the patient demographics are similar in the 2 study groups, so we feel that bias introduced by the long inclusion period was unlikely to be present. We do not have 90-day mortality because the patients we included in this study were enrolled across 15 years, and we were not able to follow up the earlier patients. Because we collected data from clinical records, we did not obtain samples to analyze cytokines or chemokines, Inflammatory markers such as CRP were available in some records, but not all, therefore due to the incomplete data, statistics were not performed. Lactate levels were also only measured for some patients, so we could not use lactate levels for analysis.

Combination of routine and CRRT therapy has an advantage over routine therapy alone for HS treatment. It can more effectively reduce body temperature, inhibit the inflammatory cascade, decrease serum concentrations of toxic metabolites, more quickly rectify disturbances of water and electrolytes, lessen acid/base imbalance and maintain homeostasis, actions that are helpful in improving HS-related abnormalities and reducing HS-related mortality.

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