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The significance of mild hypothermia therapy on patients with successful resuscitation of cardiac arrest

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Abstract. – OBJECTIVE: To investigate the clinical significance of mild hypothermia therapy in patients with resuscitation of cardiac arrest and analyze the possible molecular mechanism.

PATIENTS AND METHODS: Ninety-six patients with successful resuscitation of cardiac arrest in ICU were hospitalized from June 2009 to July 2014. They were divided into a control group (n=37 cases) and an observation group (n=59 cases). All patients received high-grade life support treatment immediately after resuscitation. The treatment for the control group was combined with normal temperature treatment while the treatment for the observation group was combined with mild hypothermia therapy.

RESULTS: 1. Glasgow coma scale (GCS) scores of the patients in the two groups increased gradually after treatment as the APACHE II scores decreased. Comparisons within the group showed significant differences ($p < 0.05$). The GCS scores of the observation group were significantly increased compared to those in the control group, and the APACHE score decreased significantly. The differences between the groups were statistically significant ($p < 0.05$). 2. The serum lactic acid, sCD14, S100 β protein and TNF-α level of patients in two groups all decreased after treatment. The difference was statistically significant ($p < 0.05$ =. 3. The 24h and 7d survival rates of patients in the observation group are higher than that in the control group ($p < 0.05$).

CONCLUSIONS: The early treatment of hypothermia, can improve the outcome of patients with cardiac arrest.

Key Words:
Mild hypothermia, Cardiac arrest, Recovery, Glasgow coma scale (GCS), APACHE score, Lactic acid, Endotoxin receptor, S100 β protein, Tumor necrosis factor-α, Survival rate.

Introduction

Cardiac arrest is a sudden heart pumping dysfunction within 24h, manifested as a loss of consciousness, arterial pulse disappearance and respiratory arrest. According to statistics, the number of patients that die of cardiac arrest each year in the world is as high as 1.2 billion, accounting for 23.5%-41.3% of the cause of death[1]. Cardiac arrest resuscitation guidelines point out that time is the most important factor to improve the success rate of recovery. The success rate of recovery can be increased by 52.6 to 82.4% with every shorten minute[2]. According to research studies, it is found that myocardial ischemia-reperfusion injury, pulmonary infection and edema are the most important reasons for the death of after recovery[3]. At present, scholars believe that sustained damage from the body hypoxia and ischemia, energy metabolism disorder, the development process of the translocation of gut-derived endotoxin, and inflammatory responses may be involved in the mechanism of the disease. Early advanced life support treatment for heart, brain, lung, liver and other important organs can be effective for preventing the deterioration of the disease[4]. More researchers are paying attention to the hypothermia treatment. But a lot of studies are still limited to animal models and its clinical application is limited[5]. On the premise of mature technology, we treat cardiac arrest patients with mild hypothermia treatment that was successful and discuss the potential molecular mechanism.

Patients and Methods

Ninety-six cases of patients diagnosed of cardiac arrest were admitted to our ICU from June 2009 to July 2014. After the consents of our hospital ethics committee and patients and family members, the patients were divided into a control group (n=37 cases) and the observation group (n=59 cases). Twenty-one cases of male and 16 cases female were in the control group. Ages

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range from 43 to 75 years old with the average age of (56.4 ± 7.6) years old. The causes of cardiac arrest were 23 cases of rapid arrhythmia such as ventricular fibrillation, nine cases of severe heartbeat bradycardia and five cases of cardiac pump failure and severe respiratory dysfunction and other diseases. The recovery times are 5 to 46 minutes with the average (16.3 ± 4.2) minutes. Twenty-nine cases were conducted with tracheal intubation and eight cases of trachea incision. Thirty-one males and 28 females were in the observation group. Their ages were 39-81 years old with the average of (57.3 ± 6.4) years old. Thirty-six cases hade rapid arrhythmia, 17 cases were severe bradycardia and six cases had other issues. The recovery time was 3 to 51 minutes on the average of (17.5 ± 3.6) minutes. 43 cases underwent tracheal intubation and 16 cases had incision of the trachea. The gender, age, arrest, and the recovery time of artificial airway of patients in the two groups showed no significant difference ($p > 0.05$).

Inclusion criteria: (1) Older than 18 years old; (2) Consistent with the diagnostic criteria of cardiac arrest; (3) Successful resuscitation of cardiac arrest in the first occurrence; (4) Sign the informed consent.

Exclusion criteria: (1) Pregnancy; (2) Multiple organ failure 24h after resuscitation; (3) Severe underlying diseases such as heart failure, respiratory failure, renal failure, cerebral edema, brain death, liver function failure which cannot be corrected; (4) Malignant tumors and patients with the expected survival time less than 1 month; (5) Patients with severe mental illness and who refuse to participate in the study.

Methods

All patients received early advanced life support treatment immediately after successful resuscitation. The details were as follows: (1) treatment of primary disease, such as vascular reperfusion therapy for acute myocardial infarction, standard medicine therapy of heart failure, antiarrhythmic therapy, catheter ablation and pacemaker treatment for malignant arrhythmia, respiratory function improvement treatment for severe respiratory dysfunction. Basic treatments, such as anti-inflammation, anti-acid, awaking, dehydration, intracranial pressure control, maintenance of water electrolyte and acid-base balance treatment, and ECG monitoring. Patients in the control group were treated with normal treatment. The rectal temperature was set with 37.5°C as the standard. Reasonable selection of physical and drug cooling, can be selected for elevated temperature. The patients in the observation group received mild hypothermia treatment. Patients were treated with mild hypothermia therapy 2-4 hours after the restoration of spontaneous circulation. Low-temperature inducement were conducted with infusion of 1000 ml 4°C normal saline and computer controlled cooling blankets. The cooling rate was controlled by 0.5-1°C/h. The anal temperature was controlled with 32 to 34°C and maintained for 24 hours. Rewarming was used with the spontaneous rewarming method. The rewarming was an average of eight hours in time and 37-37.5°C in temperature.

The difference of 0h, 8h, 16h, 24h Glasgow coma scores and APACHE scores of the patients in the two groups were analyzed as were the difference in expression level of serum lactic acid, serum endotoxin receptor (sCD14), serum S100 protein and TNF-α. The differences in survival rates after resuscitation were also compared between the two groups.

The GCS score has three aspects including eye response, language reaction and body movement with three degrees including mild[13-14], moderate[9-12] and severe coma[3-8]. The APACHE scoring system consists of the acute physiology score (APS score), age, and chronic health evaluation. The highest score is 71 points. The higher the score, the more severe the disease will be. Lactic acid was measured in the elbow venous blood by Vitros-350 dry chemistry analyzer, (New Brunswick, NJ, USA). Johnson & Johnson provided the reagent kit. It was operated in strict accordance with the instructions. The normal value of serum lactic acid ranges from 0.7 to 2.1 mmol/L. > 2.1 mmol/L was judged as positive. The sCD14, S100 β protein and the content of TNF-α protein of patients in both groups were detected by double-antibody sandwich ELISA.

Statistical Analysis

All data were analyzed using the SPSS 19 software (SPSS Inc., Chicago, IL, USA). ($\chi^2 \pm s$) was adopted for the measurement data. Comparison between the groups was analyzed using the *t*-test. Enumeration data were marked using the number of cases or (%). Comparison between groups was analyzed with using χtest. $p < 0.05$ means that the difference was statistically significant.

Table I. Comparison of GCS score and APACHE score of patients in two groups at different time

Group		Control group	Observation group	*t*	*p*
GCS score	0h	10.5±1.2	10.2±1.3	0.526	0.417
	8h	11.3±1.6	12.4±1.5	2.635	0.038
	16h	12.7±1.3	13.5±1.7	2.845	0.034
	24h	13.6±1.9	14.8±1.6	3.201	0.025
APACHE II score	0h	56.8±5.4	58.6±6.3	0.928	0.634
	8h	47.7±8.2	41.3±7.5	2.415	0.039
	16h	39.5±9.3	32.4±6.6	2.638	0.032
	24h	32.1±5.6	21.8±7.5	3.625	0.024

Result

Comparison of GCS Score and APACHE Score of Patients in two Groups at Different Time Points

Differences of GCS score and APACHE score of the patients in two groups at 0h were not significant ($p > 0.05$). The GCS scores in the two groups increased after treatment. The APACHE II scores decreased. The differences between the groups were statistically significant ($p < 0.05$). The GCS score of the observation group increased significantly compared to that of the control group. The APACHE II scores were significantly reduced. The differences between the groups were statistically significant ($p < 0.05$) (Table I).

Comparison of the Serum lactic Acid, sCD14, S100 β protein and TNF-α Levels of Patients in Two Groups

The differences in the serum lactic acid, sCD14, S100 β protein and TNF-α levels of patients in the two groups were not statistically significant before treatment ($p > 0.05$). The patients' index in the two groups decreased after treatment, and those in the observation group decreased more significantly than that in the control group. The differences were statistically significant ($p < 0.05$) (Table II).

Comparison of Survival Rate of Patients in the two Groups after Resuscitation

The survival rate of 24h and 7d of patients in the observation group were significantly higher than that of the control group. The differences were statistically significant ($p < 0.05$). While the difference in the survival rate of 6m for patients in the two groups was not statistically significant ($p > 0.05$) (Table III).

Discussion

A growing number of studies point out that mild hypothermia therapy can reduce and prevent brain cells, necrosis, and apoptosis during the ischemia and after recovery[6]. With the aggravation of hypoxia and ischemia, energy metabolism of the brain cells may be reduced or even interrupted in a short period. Cells transfer from the aerobic metabolism to anaerobic metabolism. Intracellular inorganic phosphate, lactate, hydrogen ions and calcium accumulation increase the cell edema, degeneration and inflammatory reaction that block the cell signal transduction pathway

Table II. Comparison of the serum lactic acid, sCD14, S100 β protein and TNF-α levels of patients in two groups

Group		Control group	Observation group	*t*	*p*
Lactic acid (mmol/L)	before treatment	6.8±1.3	7.1±1.5	0.367	0.204
	after treatment	4.5±1.2	2.8±1.1	3.925	0.017
sCD14 (ug/ml)	before treatment	1.6±0.2	1.8±0.3	0.524	0.368
	after treatment	0.7±0.3	0.3±0.1	4.025	0.013
S100 β (pg/ml)	before treatment	4.3±0.6	4.6±0.7	0.958	0.417
	after treatment	2.5±0.4	1.2±0.3	3.529	0.021
TNF-α (pg/ml)	before treatment	356.2±45.6	364.9±51.2	0.419	0.358
	after treatment	234.8±36.4	127.5±26.9	4.125	0.012

Table III. Comparison of survival rate of patients in the two groups after resuscitation [cases(%)].

Group		Control group	χ^2	p
Cases	37	59		
24h	29/37 78.4	52/59 88.1	4.526	< 0.001
7d	24/29 82.8	48/52 92.3	4.138	< 0.001
6m	22/24 91.7	45/48 93.8	0.526	0.957

and interrupt protein synthesis. It will induce secondary multiple organ dysfunction or failure syndromes finally after recovery[7,8].

Most previous studies focused on the animal model of cardiac arrest. They discuss the related inflammatory reaction process and hold the opinion that sustained and stable expression of the cell mediator and cytokine can appear at the early stage of ischemia-reperfusion injury, such as TNF-α and IL-1, mainly highly expressed in astrocytes, microglia and endothelial cells which can maintain at a high the level for about 5 days. The induction of the immune system and complement system dysfunction will increase the number of neutrophils, monocytes, and macrophages and aggravate brain edema through the blood-brain barrier[9,10]. Pathological brain tissue and lung tissue of the recovery animal model after sudden death were observed. It was found that the brain and lung edema decreased for the animals who received mild hypothermia treatment at an early stage. The expression of inflammatory factors also reduced significantly[11,12]. Hypothermia treatment proved to be effective in reducing the intracranial pressure by intracranial pressure measurement in clinical practice and relieving cerebral edema, improving nerve function and the long-term prognosis[13]. In addition, with the ischemia-reperfusion process, it can also produce a large number of free radicals. While mild hypothermia treatment can inhibit the process, decrease the free radicals-dependent oxidative stress and reduce the degree of injury of cells[14,15]. Some scholars have pointed out that the blood coagulation function of the body after the recovery can increase fiber formation and microvascular congestion risk in the heart and brain. While mild hypothermia treatment could interfere with the amount, function and coagulation process of platelet, which will improve the recovery of heart and brain function improvement and survival rate[16].

We come to a conclusion through the controlled clinical trials that are based on a certain number of samples and balance confounding factors between the groups. The GCS scores of the patients in the two groups increased after treatment while the APACHE II scores increased. The GCS scores of observation group were higher than that of the control group, and the APACHE scores decreased significantly. There were significant differences among the groups. Serum lactic acid, sCD14, S100 β protein and TNF-α levels of patients in two groups decreased after treatment. The index of the observation group declined more significantly than that of the control group. The differences were statistically significant. The survival rate of 24h and 7d of patients in the observation group were significantly higher than that of the control group. The differences were statistically significant. While the difference in the survival rate of 6m for patients in the two groups was not statistically significant.

The increased intestinal permeability in patients after recovery increased due to the loss of the intestinal mucosal barrier and intestinal ischemia-reperfusion injury that cause the intestinal bacteria and endotoxin translocation. The infection occurred after resuscitation informs a second struck, which can up-regulate the expression of endotoxin receptor and improve the sensitivity of the body endotoxin[17,18]. CD14 is one of the primary endotoxin receptors. Its primary role is to mediate the activation of CD14 negative cells by lipopolysaccharide, such as endothelial cells, epithelial cells and smooth muscle cells to express a large number of adhesion molecules, to relieve inflammatory cytokines and enhance the inflammatory effect of lipopolysaccharide. Studies have shown that elevated levels of sCD14 have a high correlation with the severity of illness and prognosis because up-regulation of sCD14 expression enhanced the sensitivity of endotoxin and inflammatory reaction in the body. The complex transcription mechanism of normal brain cells regulates the expression level of S100 protein accurately. The integrity of blood brain barrier makes sure that it only appears in the

cerebrospinal fluid with a very low level in serum. When cardiac arrest happens, brain ischemia, hypoxia, edema, and necrosis will result in neuronal and glial cell injury. At the same time, the soluble S100 β protein appears in the cerebrospinal fluid by intercellular fluid and into the blood circulation through the destruction of the blood-brain barrier because of the blood-brain barrier permeability increase or damage. The S100 β protein can reflect injuries and deaths of the glial cell in central nervous system nerve injuries and deaths and studies have shown that S100 β protein involved in the early pathophysiological process of pathogenesis of cerebral infarction[19,20].

Conclusions

The first use of the hypothermia treatment can significantly improve the clinical effect of patients with cardiac arrest. This may be related to reducing further the serum lactic acid, sCD14, S100 β protein and TNF-α levels and is worthy of clinical application and promotion. Early use of mild hypothermia therapy has been recommended for the cardiopulmonary cerebral resuscitation guidelines in many countries. But the mild hypothermia therapy still has many problems, the selection of indications, cooling methods, duration and prevention of the complications need further exploration.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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