

Review Article

Effects of mild hypothermia therapy on oxygen free radicals and hemodynamics in patients with craniocerebral injury

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Abstract: Objective: To investigate the effects of mild hypothermia therapy on free radicals and hemodynamics in patients with craniocerebral injury. Methods: Sixty-nine patients with craniocerebral injury admitted to Xintai City People's Hospital from July 2016 to September 2018 were enrolled, and assigned to a mild hypothermia group (n=37) and a control group (n=32) according to treatment methods. The control group was treated with conventional treatment methods, while the mild hypothermia group was treated with mild hypothermia therapy based on the treatment on the control group. The clinical efficacy, neural functional recovery, and complications of the patients were analyzed, and the oxygen free radicals, intracranial pressure, and hemodynamics of the patients before and after treatment were detected. Results: After 3 months of treatment, the mild hypothermia group got a better Glasgow outcome scale score than the control group, and after treatment, the mild hypothermia group showed a more significant decrease than the control group in neurological function score. In addition, the mean blood flow velocity of the common carotid artery, the mean volumetric blood flow velocity of it, and the maximum blood flow velocity of it in the mild hypothermia group were significantly higher than those in the control group. Moreover, after treatment, the intracranial pressure in the mild hypothermia group declined more significantly than that in the control group, and the mild hypothermia group showed significantly lower malondialdehyde, lipid peroxide and hydroxyl radical levels than those in the control group. After treatment, the superoxidedismutase level in the mild hypothermia group increased more significantly than that in the control group. Conclusion: Mild hypothermia is effective for the treatment of craniocerebral injury, because it can significantly reduce the oxygen free radical level and stabilize cerebral circulation function. Therefore, it is worthy of clinical application and promotion.

Keywords: Craniocerebral injury, mild hypothermia, free radical, hemodynamics, intracranial pressure

Introduction

The incidence of craniocerebral injury accounts for 10-15% of all body injuries. Accidents including traffic accidents, industrial accidents, and high falling accidents can all give rise to this injury, and the injury is characterized by high incidence, sudden occurrence, and fast progression [1, 2]. According to statistics, more than 50,000,000 people suffer from traumatic brain injury (TBI) every year in the world, and about half of the world's population has experienced one or more times of TBI. The incidence of TBI was the second highest in that of the systemic trauma, but its mortality and disability risk are the first, which seriously threatens

the life and life quality of patients. Therefore, finding appropriate treatment methods for patients with craniocerebral injury to improve the cure rate and reduce disability rate has been the focus of the current research [3-5].

Hyperthermia is often secondary to craniocerebral injury, and the brain tissue temperature under craniocerebral injury can rise to 38~43°C, further aggravating brain tissue injury. Meantime, the high temperature may cause hypermetabolism in the body and aggravate the symptoms of ischemia and hypoxia [6, 7]. Mild hypothermia can relieve cerebral ischemia and hypoxia, and decrease the release of endogenous inflammatory factors, which is con-

ducive to maintaining the aerobic metabolism of nerve cells and alleviating the damage to the body caused by anaerobic metabolic products [8, 9]. Previous studies have confirmed that brain injury brings about the release of a large number of free radicals that damage cells and aggravate tissue damage through lipid peroxidation, protein oxidation, hydrolysis, adenosine triphosphate (ATP) depletion, and DNA damage [10, 11]. The changes of cerebral hemodynamics are important pathological changes after craniocerebral injury, and ischemia, edema, vasospasm, and hematoma compression in cerebral tissues can all lead to the decrease of cerebral blood flow velocity and blood flow, resulting in cerebral ischemia, aggravating craniocerebral injury, and even bringing about cerebral infarction [12, 13].

Although the efficacy of mild hypothermia therapy on craniocerebral injury has been proved, there are few studies on its effect on oxygen free radicals and hemodynamics in patients with craniocerebral injury. This study compared mild hypothermia therapy and conventional treatment to explore the effects of mild hypothermia therapy on oxygen free radicals and cerebral hemodynamics in the treatment of craniocerebral injury (acute cerebral edema) in patients, so as to understand the protective mechanism of mild hypothermia on the brain to provide reference for the treatment of patients with craniocerebral injury.

Materials and methods

General data

Methods: Sixty-nine patients with craniocerebral injury admitted to Xintai City People's Hospital from July 2016 to September 2018 were enrolled, and assigned to a mild hypothermia group and a control group according to treatment methods. The control group (n=32) was treated with conventional treatment methods, while the mild hypothermia group (n=37) was treated with mild hypothermia therapy based on the treatment on the control group. The mild hypothermia group consisted of 21 males and 16 females between 24 and 59 years old, with an average age of 41.29 ± 10.56 years, and the control group consisted of 22 males and 10 females between 22 and 61

years old, with an average age of 40.82 ± 11.31 years. The inclusion criteria of the patients were as follows: Patients diagnosed with craniocerebral injury according to CT and other examinations, patients without severe damage to internal organs, patients willing to receive this treatment regime, patients between 18-60 years old, and admitted to hospital 6 hour after suffering from craniocerebral injury, and patients with detailed clinical data. This study did not violate ethics and morals, and it was carried out after approval documents had been obtained from the Ethics Committee of Xintai City People's Hospital. Each patient voluntarily signed an informed consent form after understanding this study. The exclusion criteria were as follows: Patients with primary intracranial disease, encephalic angioma, severe cardio-cerebrovascular disease, or severe inflammation, pregnant women, lactating women, patients allergic to used drugs, patients who had received calcium antagonists, patients intolerant to therapeutic drugs and methods of the study, patients comorbid with fatal thoracic or abdominal trauma, great vessel rupture, spinal fractures, concomitant nervous lesion or other severe trauma, and patients comorbid with severe internal underlying diseases in important organs such as heart, liver, and kidney, and patients with congenital cognitive impairment.

Treatment methods

Patients in the control group were monitored in terms of vital signs such as body temperature, heart rate, respiration, and blood pressure in a neurosurgery intensive care unit, and their routine blood indexes, blood electrolytes, blood gas, hepatic and renal function, blood glucose, myocardial enzyme and others were examined and analyzed regularly. Their Glasgow coma scale (GCS) scores at admission were recorded, and they were treated routinely with therapies such as dehydration, hemostasis, anti-inflammation, and drugs nurturing nerves. They were also treated with tracheotomy if necessary. Patients with operative indications were given conventional treatment such as oxygen inhalation, craniotomy, and puncture drainage after emergency operation. The mild hypothermia group was treated with mild hypothermia therapy based on the treatment on the control group. They were treated with physical cooling

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and drug cooling after being admitted or operated. Under the assistance of a ventilator, each patient received continuous cooling with a semiconductor ice blanket machine, and was treated with 100 ml normal saline + 100 mg vecuronium at 5-10 ml/h, and 100 ml normal saline + 100 mg morphine hydrochloride at 10 ml/h. If necessary, they were given ice compress and frozen infusion at their head, neck, outer, and inguinal site, and treated with ice water enema or gastric irrigation with cool water to lower their anal temperature to below 35°C within 4-12 h. After 14 days of the temperature lower than 35°C, their anal temperature was lifted to achieve normal temperature naturally at a speed of 1°C every 4-6 h. Ice blanket machine can be adopted to control the temperature resumption speed.

Outcome measures and detection methods

Efficacy evaluation criteria: The efficacy was evaluated according to the Glasgow Outcome Scale (GOS) after three months of treatment [14]. In GOS, 5 points indicated that the patient recovered well and returned to normal life, despite mild defect; 4 points indicated that patient had mild disability, but could live independently, and could work under protection; 3 points indicated that the patient had severe disability in a conscious state and need care in daily life; 2 points indicated that the patient was in a vegetative status only with minimal reaction (such as eye opening with the sleep/wakefulness cycle), and 1 point indicated that the patient was dead.

Neurological function score: The neurological function of the patients was evaluated using the National Institutes of Health Stroke Scale (NIHSS) [15]. The scale run between 0 and 42 points, and covered consciousness, gaze, facial paralysis, lower-limb muscular strength, lower-limb muscular strength, ataxia, aphasia, dysarthria, sensation, vision, neglect, and distal limb function. A lower NIHSS score indicated better neural functional recovery.

Evaluation of oxygen free radicals and cerebral hemodynamics

The oxygen free radicals and cerebral hemodynamics of the patients were analyzed 1 day before treatment and 7 days after treatment. (1) Oxygen free radicals: 5 mL of peripheral

fasting venous blood was sampled from each patient, and centrifuged to collect the serum. The malondialdehyde (MAD) and superoxide-dismutase (SOD) of the patients were detected using the barbituric acid method and the improved hydroxylamine hydrochloride method, respectively, and their lipid peroxide (LPO) and hydroxyl radical (OH) were detected using the enzyme-linked immunosorbent assay (ELISA) and chemiluminescent immunoassay, respectively. A blank well and a well for samples to be detected were set, respectively. Sample diluents (40 μ l) were added into the well for samples to be detected in the enzyme-labeled coating plate, and then 10 μ l samples to be detected were added into the well (the sample was diluted by 5 times). The samples were added to the bottom of the plate, without touching the well wall as much as possible, and shaken gently. The plate was sealed and cultured at 37°C for 30 min, and 30 times concentrated washing liquid was diluted with distilled water 30 (20 times of 48T) for later use. The sealing film was carefully removed, and the liquid was discarded. Each well was spun dry, and let to stand for 30 s after being filled with washing liquid. The washing and drying were repeated five times, and then the plate was patted dry. Subsequently, each well except the blank well was added with 50 μ l conjugate reagent, and the plate was cultured at 37°C for 20 min, and washed. Each well was added with 50 μ l developer A and 50 μ l developer B in order, shaken gently, and developed in the dark at 37°C for 15 min. Finally, each well was added with 50 μ l stopping solution to stop the reaction (blue turned to yellow at this time). The optical density (OD) of each well at 450 nm was measured under zeroing of the blank well. The measurement shall be carried out within 15 min after the stopping solution was added. (2) Cerebral hemodynamics: The mean blood flow velocity of the common carotid artery (V_{mean}), the minimum blood flow velocity of it (V_{min}), the mean volumetric blood flow velocity of it (Q_{mean}), and the maximum blood flow velocity (V_{max}) of the patients were determined using a cerebral circulation analyzer.

Statistical analysis

In this study, the data were statistically analyzed using SPSS22.0 (SPSS Inc., Chicago, the

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Table 1. Clinical baseline data of the two groups

Factor	The mild hypothermia group (n=37)	The control group (n=32)	χ^2/t	P-value
Sex			1.051	0.305
Male	21 (56.76)	22 (68.75)		
Female	16 (43.24)	10 (31.25)		
Age (Y)	41.29±10.56	40.82±11.31	0.179	0.859
BMI (kg/m ²)	24.45±1.34	23.89±1.69	1.534	0.130
Place of residence			0.048	0.826
Urban area	16 (43.24)	13 (40.63)		
Rural area	21 (56.76)	19 (59.38)		
Smoking history			1.399	0.237
Yes	8 (21.62)	11 (34.38)		
No	29 (78.38)	21 (65.63)		
Exercise habit			1.466	0.226
Yes	13 (35.14)	7 (21.88)		
No	24 (64.86)	25 (78.13)		
History of alcoholism			0.313	0.576
Yes	9 (24.32)	6 (18.75)		
No	28 (75.68)	26 (81.25)		
GCS score	5.37±2.61	5.45±2.54	0.129	0.898
Cause of injury			0.604	0.739
Traffic injury	21 (56.76)	17 (53.13)		
Blunt injury	7 (18.92)	9 (28.13)		
Falling injury	9 (24.32)	8 (25)		
Time from injury to treatment	0.65±0.37	0.71±0.43	0.623	0.535
Past medical history			2.077	0.354
Hypertension	4 (10.81)	5 (15.15)		
Diabetes mellitus	6 (16.22)	3 (9.09)		
Hyperlipidemia	3 (8.11)	6 (18.18)		
Disease type			0.819	0.845
Diffuse axonal injury	9 (24.32)	7 (21.21)		
Subdural hematoma	13 (35.14)	10 (30.3)		
Subarachnoid hemorrhage	7 (18.92)	9 (27.27)		
Ventricular hemorrhage	8 (21.62)	6 (18.18)		

Table 2. Comparison of GOS score between the control group and the mild hypothermia group [n (%)]

Item	The mild hypothermia group (n=37)	The control group (n=32)	χ^2 value	P-value
1 point	4 (10.81)	12 (37.5)	11.65	0.02
2 points	6 (16.22)	4 (12.5)		
3 points	4 (10.81)	5 (15.63)		
4 points	5 (13.51)	6 (18.75)		
5 points	18 (48.65)	5 (15.63)		

United States), and enumeration data were expressed by rate (%) and analyzed using the

χ^2 test. Measurement data were expressed by the mean \pm standard deviation ($x \pm sd$), and analyzed using the independent-samples T test. $P < 0.05$ suggested a significant difference.

Results

Clinical baseline data of the two groups

There was no significant difference between the mild hypothermia group and the control group in baseline data including sex, age, body mass index (BMI), place of residence, exercise habit, GCS score, cause of injury, time of treatment due to injury, previous medical history, and disease type ($P > 0.05$, **Table 1**).

Comparison of GOS score between the mild hypothermia group and the control group

All the patients were followed up for 3 months to analyze their GOS score, and it was turned out that GOS score of the mild hypothermia group was better than that of the control group ($P < 0.05$, **Table 2**).

Comparison of neurological function score between the two groups before and after treatment

Comparison between the two groups in neurological function score before and after treatment showed that before treatment, the two groups had no big difference in neurological function score ($P > 0.05$), while after

treatment, both groups got a lower neurological function score, and the decline in the mild

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Table 3. Comparison of neurological function score between the two groups before and after treatment

Item	Before treatment	After treatment	T-value	P-value
The mild hypothermia group (n=37)	31.86±11.78	12.78±6.33	8.293	<0.01
The control group (n=32)	32.04±10.67	17.39±8.43	6.26	<0.01
t-value	0.066	2.589		
P-value	0.947	0.012		

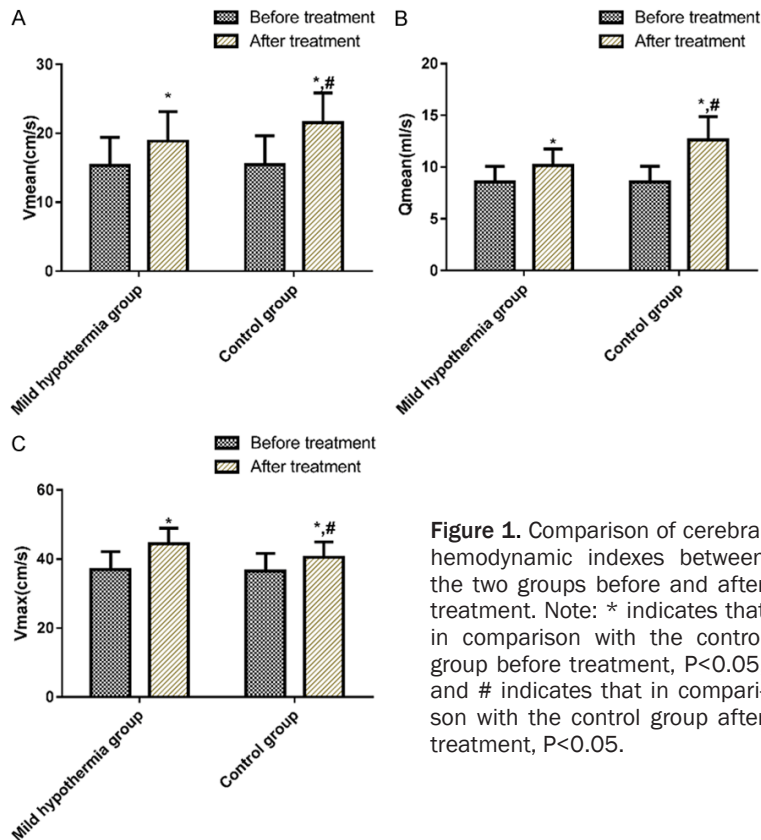


Figure 1. Comparison of cerebral hemodynamic indexes between the two groups before and after treatment. Note: * indicates that in comparison with the control group before treatment, $P < 0.05$, and # indicates that in comparison with the control group after treatment, $P < 0.05$.

hypothermia group was more significant than that in the control group ($P < 0.05$, **Table 3**).

Comparison of cerebral hemodynamic indexes between the two groups

Before treatment, there was no significant difference between the two groups in V_{mean} , Q_{mean} , and V_{max} (all $P > 0.05$), while after treatment, the V_{mean} , Q_{mean} , and V_{max} levels of the two groups dramatically increased, and the levels of the mild hypothermia group were remarkably higher than those of the control group ($P < 0.05$, **Figure 1**).

Comparison of intracranial pressure between the two groups before and after admission

Comparison between the two groups in intracranial pressure before and after treatment

showed that before treatment, the two groups were not significantly different in intracranial pressure ($P > 0.05$), while after treatment, the intracranial pressure of both groups significantly declined, and the decline in the mild hypothermia group was more significant than that in the control group ($P < 0.05$, **Table 4** and **Figure 2**).

Comparison of oxygen free radical level between the two groups before and after treatment

Comparison between the two groups in oxygen free radical level showed that before treatment, the two groups were not significantly different in oxygen free radical level ($P > 0.05$), while after treatment, the MAD, LPO, and OH levels of the mild hypothermia group decreased, and dramatically

lower than those of the control group ($P < 0.05$), and the SOD level of the two groups remarkably increased, and the SOD level of the mild hypothermia group was remarkably higher than that of the control group ($P < 0.05$, **Figure 3**).

Comparison of complications between the two groups

The mild hypothermia group showed a total incidence of complications of 13.51%, with pulmonary infection in 1 patient (2.7%), intracranial infection in 2 patients (5.41%), significantly abnormal heart rhythm in 1 patient (2.7%), and gastrointestinal hemorrhagic stress ulcer in 1 patient (2.7%), and the control group showed a total incidence of complications of 40.63%, with pulmonary infection in 3 patients (9.38%),

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Table 4. Comparison of intracranial pressure between the two groups before and after treatment

Item	Before treatment	After treatment	t	P-value
The mild hypothermia group (n=37)	190.45±14.69	158.35±14.42	9.129	<0.01
The control group (n=32)	191.34±14.26	184.27±10.64	2.304	0.024
t-value	0.264	8.18		
P-value	0.792	<0.01		

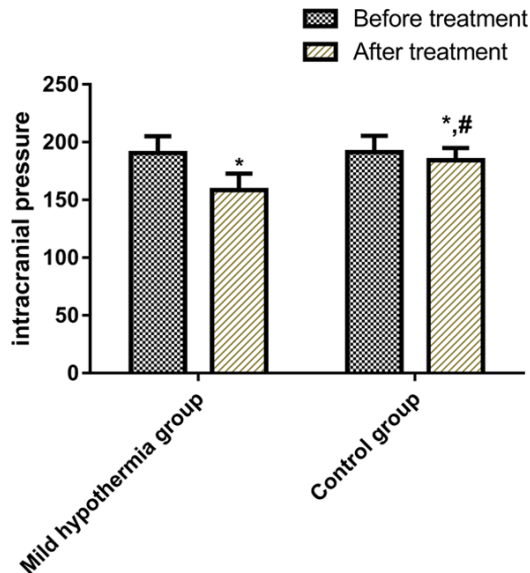


Figure 2. Comparison of intracranial pressure between two groups before and after admission. Note: * indicates that in comparison with the control group before treatment, $P < 0.05$, and # indicates that in comparison with the control group after treatment, $P < 0.05$.

intracranial infection in 4 patients (12.5%), significantly abnormal heart rhythm in 2 patients (6.25%), and gastrointestinal hemorrhagic stress ulcer in 4 patients (12.5%), so the incidence of complications in the mild hypothermia group was significantly lower than that in the control group ($P < 0.05$, **Table 5**).

Discussion

Craniocerebral injury is a common clinical trauma, which occurs suddenly and progresses rapidly [16, 17]. It brings about damage to the blood-brain barrier and release of many coagulating substances, which gives rise to systemic or local coagulation dysfunction. Moreover, brain tissue injury increases intracranial pressure and contributes to insufficiency of cerebral blood supply, and brain tissues are further subjected to hypoxia, ischemia and the

like, which forms a vicious circle, and increases mortality and disability [18-20]. Therefore, it is particularly important to effectively diagnose and treat patients with craniocerebral injury at the early stage in controlling the development of the disease and reducing their mortality rate [21, 22].

Mild hypothermia therapy is a hot research topic in recent years, which mainly lowers the body temperature through physical cooling and maintains it within a specific range, thus providing support for the treatment of diseases and improvement of prognosis [23, 24]. A study by Flynn et al. [25] concluded that hypothermia therapy could lower the intracranial pressure of patients with severe craniocerebral trauma and alleviate their cerebral oxygen tension, and a study by Chen et al. [26] pointed out that mild hypothermia could promote the long-term survival of newborn dentate gyrus cells after craniocerebral trauma by weakening pro-apoptotic microenvironment. According to the above, mild hypothermia therapy is obviously beneficial to patients with craniocerebral injury. In this study, the prognosis, neurological function score and complications of the two groups were compared, and it was found that after 3 months of treatment, the mild hypothermia group got a better GOS score than the control group, and the neurological function score decline in the mild hypothermia group was much significant than that in the control group. In addition, it was also found that the total incidence of complications in the mild hypothermia group was dramatically lower than that in the control group. It indicated that mild hypothermia was effective for the treatment of patients with craniocerebral injury, and it was beneficial to relieving the neurological function damage and conducive to the prognosis of patients.

Oxygen free radicals are metabolites of the body. When the body is damaged to a certain extent, the damage can cause metabolic dysfunction, anoxia, and ischemia, resulting in the

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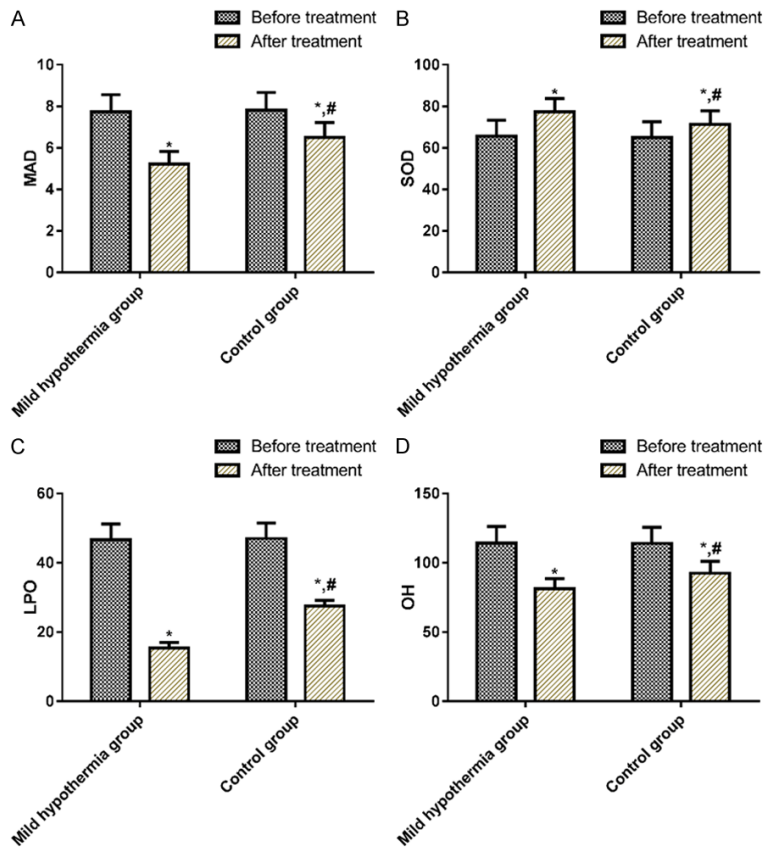


Figure 3. Comparison of oxygen free radical level between two groups before and after treatment. Note: * indicates that in comparison with the control group before treatment, $P < 0.05$, and # indicates that in comparison with the control group after treatment, $P < 0.05$.

formation of oxygen free radicals, damaging the biomembrane system, and aggravating the damage degree of the body [27, 28]. The scavenging function of oxygen free radicals reflects the ability of tissue repair and disease recovery, so improving the scavenging ability against oxygen free radicals is especially important for recovery [29]. Therefore, we compared the MAD, LPO, OH, and SOD levels of the two groups before and after treatment, finding that after treatment, the mild hypothermia group showed significantly decreased MAD, LPO, and OH levels, and the levels in the mild hypothermia group were significantly lower than those of the control group. We also found that after treatment, both groups showed increased SOD level, and the level in the mild hypothermia group was much higher than that in the control group. It indicated that mild hypothermia therapy could lower the oxygen free radical level in patients with craniocerebral injury.

Circulatory disturbance is an important pathophysiologic foundation for secondary brain injury and cerebral ischemia and hypoxia. Our study revealed that the cerebral hemodynamics was obviously disordered after craniocerebral injury. Blood flow velocity and blood flow volume are common indicators for cerebral blood supply assessment. The results of this study showed that after treatment, the V_{mean} , Q_{mean} , and V_{max} levels of patients receiving mild hypothermia therapy were higher than those of patients receiving conventional treatment, which suggested that for patients with craniocerebral injury, mild hypothermia therapy was more helpful in treating the cerebral hemodynamic disorder, alleviating secondary craniocerebral injury, stabilizing cerebral circulation function, and protecting the brain.

Although this study confirmed that mild hypothermia was effective for patients with craniocerebral injury, it still has some deficiencies. The regulation mechanisms of MAD, LPO, OH, and SOD in craniocerebral injury were not deeply analyzed, and the risk factors for the patients were also not explored, so there were certain design defects in the study. These deficiencies need to be addressed in the future to better corroborate the research results of this study.

To sum up, mild hypothermia is effective for the treatment of patients with craniocerebral injury in clinical practice, because it can significantly lower the oxygen free radical level and stabilize cerebral circulation function. Therefore, it is worthy of clinical application and promotion.

Disclosure of conflict of interest

None.

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Table 5. Comparison between the mild hypothermia group and the control group in the incidence of postoperative complications [n (%)]

Item	The mild hypothermia group (n=37)	The control group (n=32)	χ^2 -value	P-value
Pulmonary infection	1 (2.7)	3 (9.38)		
Intracranial infection	2 (5.41)	4 (12.5)		
Significantly abnormal heart rhythm	1 (2.7)	2 (6.25)		
gastrointestinal hemorrhagic stress ulcer	1 (2.7)	4 (12.5)		
The total incidence	5 (13.51)	13 (40.63)	7.75	<0.01

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