Effects of mild hypothermia on cerebral oxygen metabolism and brain injury in patients with severe craniocerebral injury

Jiang Wang¹, Ya-Dong Yang¹, Qiu-Fang She¹, Gui-Fen Chen²

¹ Department of Critical Care Medicine, Huanggang Central Hospital in Hubei Province, Huanggang, Hubei Province, 438000
² Department of Humanities and Management, Fujian University of Traditional Chinese Medicine, Fuzhou, Fujian Province, 350122

ARTICLE INFO

Article history:
Received 18 Dec 2017
Received in revised form 28 Dec 2017
Accepted 4 Jan 2018
Available online 14 Jan 2018

Keywords:
Severe craniocerebral injury
Mild hypothermia
Cerebral oxygen metabolism
Brain injury

ABSTRACT

Objective: To investigate the effects of mild hypothermia on cerebral oxygen metabolism and brain injury in patients with severe craniocerebral injury. Methods: A total of 78 patients with severe craniocerebral injury who underwent emergency treatment in Huanggang Central Hospital between September 2015 and May 2017 were selected as the research subjects and divided into control group (n=39) and mild hypothermia group (n=39) by random number table. Control group received clinical standard large trauma craniotomy for severe craniocerebral injury, and mild hypothermia group received routine surgery and postoperative mild hypothermia therapy. The cerebral oxygen metabolism and brain injury in two groups of patients were detected immediately after admission (T0), 1 week after treatment (T1) and 4 weeks after treatment (T2). Results: At T0, there was no statistically significant difference in the levels of cerebral oxygen metabolism indexes, cerebral blood flow parameters and brain injury markers between the two groups. At T1 and T2, PO2 levels in mild hypothermia group were higher than those in control group while Da-jvO2 levels were lower than those in control group; cerebral blood flow parameters Vs and Wv levels were higher than those in control group while PI levels were lower than those in control group; brain injury markers MBP, AQP-4 and S-100B contents were lower than those in control group while BDNF contents were higher than those in control group. Conclusion: Adjuvant mild hypothermia therapy after routine surgery may further reduce the cerebral oxygen metabolism and relieve the brain injury in patients with severe craniocerebral injury.

1. Introduction

Emergency surgery is needed after severe brain trauma to remove hematomata and avoid the continuous increased intracranial pressure and even cerebral hernia formation caused by hematomata and secondary cerebral edema[1,2]. Current studies have shown that although the intracranial pressure reduction, neurotrophy and other adjuvant therapies are adopted after standard large trauma craniotomy, the aggravation of brain function injury still occurs in some patients, and it is a sign of poor prognosis. Mild hypothermia therapy has mostly been used in the treatment of cerebral infarction and other nerve injury diseases in recent years, which can reduce cerebral oxygen metabolism, decrease oxygen free radical generation and so on to reduce neuron necrosis and apoptosis, relieve cerebral edema and reduce intracranial pressure[3-5]. There is not much research about the application of adjuvant mild hypothermia therapy in the patients with severe craniocerebral trauma, mild hypothermia treatment was added in the overall treatment of such patients after standard large trauma craniotomy, and the changes in cerebral oxygen metabolism and the resulting changes in nerve function were explored in the study to provide a reference for subsequent therapy selection for similar patients, now reported as follows.
2. Information and methods

2.1 Inclusion and exclusion criteria

Inclusion criteria: (1) diagnosed with acute brain injury by emergency MRI; (2) with clear history of traumatic brain injury; (3) with the interval between the trauma and the hospitalization 4 h; (4)18-80 years old; (5) whose families signed informed consent. Exclusion criteria: (1) with history of traumatic brain injury; (2) with history of brain surgery; (3) with history of cerebral infarction; (4) with history of mild hypothermia therapy; (5) combined with systemic infectious diseases.

2.2 Case information

A total of 78 patients with severe craniocerebral injury undergoing emergency treatment in this hospital between September 2015 and May 2017 were selected as the research subjects and divided into control group (n=39) and mild hypothermia group (n=39) by random number table. Control group included 21 males and 18 females who were 28-61 years old; mild hypothermia group included 22 males and 17 females who were 26-59 years old. The basic data distribution were comparable between the two groups, and the hospital ethics committee discussed and approved the implementation of the research plan.

2.3 Therapy

Control group underwent clinical standard large trauma craniotomy for patients with severe craniocerebral injury, and received dehydration, intracranial pressure reduction, preventive anti-infection and other adjuvant therapies after operation. After mild hypothermia group underwent standard large trauma craniotomy, craniocerebral freezer was applied for mild hypothermia therapy in local injured brain, the freezer temperature was set to 32-35 °C, the mild hypothermia therapy was stopped after the intracranial pressure was restored to normal and maintained there for 24 h, and the total course of treatment lasted for about 3-7 d. After that, the temperature was gradually restored to normal brain temperature within 24 h.

2.4 Observation indexes

Immediately after admission (T0), 1 week after treatment (T1) and 4 weeks after treatment (T2), the levels of cerebral oxygen metabolism indexes of two groups of patients were determined, including cerebral oxygen partial pressure (PO2) and arterial-internal jugular venous blood oxygen content difference (Da-jvO2); the cerebral blood flow parameters were measured, including the middle cerebral arterial peak systolic velocity (Vs), pulse wave velocity (Wv) and pulsatility index (PI); the contents of peripheral blood serum brain injury markers were determined, including myelin basic protein (MBP), Aquaporin 4 (AQP-4), brain-derived neurotrophic factor (BDNF) and S-100 protein B (S-100B).

2.5 Statistical methods

Cerebral oxygen metabolism indexes, cerebral blood flow parameters and brain injury markers were input in statistical software SPSS 25.0, t test was used to calculate statistics and P<0.05 was the sign that the differences were significant statistically.

3. Results

3.1 Cerebral oxygen metabolism indexes

Comparison of cerebral oxygen metabolism indexes PO2 (mmHg) and Da-jvO2 (mL/L) levels between the two groups at different points in time was as follows: at T0, PO2 and Da-jvO2 levels were not significantly different between the two groups (P>0.05). At T1 and T2, PO2 levels in both groups were higher than those at T0 while Da-jvO2 levels were lower than those at T0; PO2 levels in mild hypothermia group were higher than those in control group while Da-jvO2 levels were lower than those in control group (P<0.05) (Table 1).

Table 1.
Comparison of cerebral oxygen metabolism index levels before and after treatment.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time point</th>
<th>PO2 (mmHg)</th>
<th>Da-jvO2 (mL/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>39</td>
<td>T0</td>
<td>9.11±0.95</td>
<td>48.29±6.14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T1</td>
<td>14.38±1.76</td>
<td>44.76±5.81†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T2</td>
<td>20.34±2.95</td>
<td>45.05±5.72†</td>
</tr>
<tr>
<td>Mild hypothermia group</td>
<td>39</td>
<td>T0</td>
<td>9.12±0.92</td>
<td>48.31±5.98</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T1</td>
<td>17.94±2.11</td>
<td>37.28±4.17†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T2</td>
<td>28.21±3.58</td>
<td>42.26±5.21†</td>
</tr>
</tbody>
</table>

Note: compared with same group at T0, †P<0.05.

3.2 Cerebral blood flow parameters

Comparison of cerebral blood flow parameters Vs (cm/s), Wv (m/ s) and PI levels between the two groups at different points in time was as follows: at T0, Vs, Wv and PI levels were not significantly different between the two groups (P>0.05). At T1 and T2, Vs and Wv levels in both groups were higher than those at T0 while PI levels were lower than those at T0; Vs and Wv levels in mild hypothermia group were higher than those in control group while PI levels were lower than those in control group (P<0.05) (Table 2).

Table 2.
Comparison of cerebral blood flow parameter levels before and after treatment.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time point</th>
<th>Vs (cm/s)</th>
<th>Wv (m/ s)</th>
<th>PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>39</td>
<td>T0</td>
<td>79.23±8.15</td>
<td>12.18±1.63</td>
<td>0.79±0.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T1</td>
<td>82.18±8.65</td>
<td>13.74±1.62</td>
<td>0.71±0.08†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T2</td>
<td>85.09±9.25</td>
<td>15.07±1.38</td>
<td>0.62±0.07†</td>
</tr>
<tr>
<td>Mild hypothermia group</td>
<td>39</td>
<td>T0</td>
<td>79.37±8.04</td>
<td>12.09±1.57</td>
<td>0.78±0.08</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T1</td>
<td>85.71±9.43</td>
<td>15.68±1.73</td>
<td>0.69±0.07†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T2</td>
<td>92.33±10.29</td>
<td>19.11±2.45</td>
<td>0.54±0.06†</td>
</tr>
</tbody>
</table>

Note: compared with same group at T0, †P<0.05.
Table 3.
Comparison of serum brain injury marker contents before and after treatment.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time point</th>
<th>MBP</th>
<th>AQP-4</th>
<th>BDNF</th>
<th>S-100B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>39</td>
<td>T0</td>
<td>20.18±2.64</td>
<td>38.48±4.51</td>
<td>13.28±1.63</td>
<td>10.29±1.74</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T1</td>
<td>17.36±1.95</td>
<td>31.27±3.29</td>
<td>16.11±1.84</td>
<td>8.37±0.91</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T2</td>
<td>13.02±1.56</td>
<td>25.48±3.11</td>
<td>20.59±2.46</td>
<td>6.18±0.75</td>
</tr>
<tr>
<td>Mild hypothermia group</td>
<td>39</td>
<td>T0</td>
<td>20.24±2.39</td>
<td>38.45±4.37</td>
<td>13.31±1.59</td>
<td>10.32±1.81</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T1</td>
<td>14.18±1.63</td>
<td>26.09±3.42</td>
<td>19.74±2.51</td>
<td>5.87±0.63</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T2</td>
<td>9.11±0.98</td>
<td>19.77±2.39</td>
<td>28.36±3.42</td>
<td>3.11±0.42</td>
</tr>
</tbody>
</table>

Note: compared with same group at T0, *P<0.05.

3.3 Brain injury markers

Comparison of serum brain injury markers MBP (mg/L), AQP-4 (ng/mL), BDNF (ng/mL) and S-100B (ng/mL) contents between the two groups at different points in time was as follows: at T0, serum MBP, AQP-4, BDNF and S-100B contents were not significantly different between the two groups (P>0.05). At T1 and T2, MBP, AQP-4 and S-100B contents in both groups were lower than those at T0 while BDNF contents were higher than those at T0; MBP, AQP-4 and S-100B contents in mild hypothermia group were lower than those in control group while BDNF contents were higher than those in control group (P<0.05), shown in Table 3.

4. Discussion

Severe craniocerebral injury is caused by the external forces on the head, and severe cerebral contusion, cerebral edema and intracranial hypertension can appear in the patients, which may cause cerebral hernia in a short time and even death in patients without timely treatment. Standard large trauma craniotomy is the main therapy for clinical severe craniocerebral injury, which is easy and safe to operate and significant in reducing intracranial pressure[6,7]. However, the intracranial pressure rebound and progressive neurologic function decline may occur in some patients after surgery, which is speculated to be closely related to the insufficient oxygen supply to injured nerve tissue and persistent hypoxic ischemic injury. The contradiction between insufficient oxygen supply and big oxygen consumption in local damaged brain tissue can directly influence the disease outcome, which is particularly significant early after the operation. How to improve the oxygen metabolism of damaged nerve tissue is the focus of the present clinical research. Mild hypothermia is a method that reduces the patients’ local body temperature to expected levels through physical means, which has been successfully applied in diseases such as cerebral infarction and hypertensive cerebral hemorrhage, reduces local brain tissue stability and can effectively reduce the its oxygen metabolism, improve cell energy metabolism, reduce oxygen free radical synthesis and eventually exert the effects such as protecting nerve cell function and restoring intercellular signaling transduction[8,9]. In this study, mild hypothermia was used as an auxiliary therapy after emergency operation for patients with severe craniocerebral injury, and the effects of this method on cerebral oxygen metabolism and nerve injury in patients were discussed.

Local cerebrovascular rupture and hemorrhage occur after severe craniocerebral injury and result in abnormal blood supply to nerve tissue in lesion area and rapid decline in cerebral blood oxygen content, and the continuous high oxygen consumption in the damaged brain tissue at this period will rapidly increase the ischemic hypoxic injury and lead to irreversible damage and even apoptosis of nerve cells[10-11]. In acute stage of traumatic brain injury, appropriate reduction of cerebral oxygen consumption can protect the injured nerve tissue, and avoid the massive production of oxygen free radicals in hypoxic state and the resulting oxidative stress injury to brain tissue. Mild hypothermia is the method that reduces local injured brain tissue temperature to 32-35 ℃, the peak of brain edema after operation lasts for about 5-7 d, so the mild hypothermia will last for a week or so time, and it will reduce the oxygen consumption of nerve tissue and relieve cerebral edema[12,13]. PO2 and Da-jvO2 are the important indicators to reflect the oxygen metabolism of nerve tissue, lower oxygen consumption leads to the increase PO2 levels in brain tissue, the oxygen consumption reduces when arterial blood flows through the brain tissue, so the oxygen content increases in venous blood, the difference of arteriovenous blood oxygen content reduces, and Da-jvO2 levels drop[14]. In this study, the differences in cerebral oxygen metabolism were compared between the two groups, and it was found that compared with that at T0, the cerebral oxygen consumption of both groups decreased at different points in time after treatment; further compared with those in control group, PO2 levels in mild hypothermia group were higher while Da-jvO2 levels were lower at T1 and T2, confirming that mild hypothermia therapy can effectively decrease the cerebral oxygen metabolism rate and lay a foundation for the cerebral functional recovery in acute phase.

Mild hypothermia also has regulating effect on the cerebral blood flow, which increases the nitric oxide content in local brain to dilate cerebral vessels and increase cerebral blood flow, antagonizes the neuron injury and even apoptosis caused by reduced cerebral blood supply, and promotes the repair of injured brain tissue after emergency operation[15,16]. The middle cerebral artery is one of the most important blood vessels to maintain normal cerebral blood supply, and its blood flow status can directly reflect the blood supply of nerve tissue. Both Vs and Wv reflect the cerebral blood flow velocity, and the higher their levels, the faster the cerebral blood flow and the more the blood supply; PI reflects cerebral vascular resistance, and the higher the PI level, the greater the vascular resistance and the less cerebral blood flow[17]. The results of this study showed that compared with those at T0, Vs and Wv levels in both groups increased while PI levels decreased at different points in time; further compared with those in control group, Vs and Wv levels in mild hypothermia group were higher while PI levels were lower at T1 and T2, it confirms that the adjuvant mild hypothermia therapy can further increase cerebral blood flow and reduce cerebral...
blood flow resistance, and this is the important foundation for brain function improvement.

Brain tissue injury and nerve function inhibition or even loss are the main manifestations of severe craniocerebral trauma, and the severity of brain injury is one of the most reliable indicators to reflect the effectiveness of clinical treatment. MBP mainly exists in oligodendrocytes, it is used to constitute the central nervous system myelin, and serum MBP content increases after the occurrence of acute nervous system injury, which is directly related to nervous demyelinating change[18]. AQP-4 widely exists in the central nervous tissue, its content is particularly abundant near the basement membrane, and animal experiment has confirmed that the 24 h after craniocerebral injury, AQP-4 expression increases in traumatic area, and its content is lower in the adjacent normal brain tissue[19]. BDNF has neurotrophic function and can promote the mitosis of neurons and repair the secondary injury of damaged nerve and tissue neurons, and its content is negatively correlated with the degree of nerve injury[20]. S-100B is a typical brain injury marker, it specifically exists in the nerve tissue, and it can be massively released into the cerebrospinal fluid and further infiltrate into the blood after brain injury[21]. The results of this study showed that compared with those at T0, MBP, AQP-4 and S-100B contents in both groups decreased while BDNF contents increased at different points in time after treatment; further compared with those in control group, MBP, AQP-4 and S-100B contents in mild hypothermia group were lower while BDNF contents were higher at T1 and T2, confirming that adjuvant mild hypothermia therapy can effectively reduce brain damage and promote nerve repair.

To sum up, it can be concluded that the adjuvant mild hypothermia therapy after emergency operation can effectively reduce cerebral oxygen metabolism, increase cerebral blood flow and reduce brain injury in patients with severe craniocerebral injury, and it is worthy of popularization and application in clinical practice in the future.

References


