Original Article

Effect of Edaravone on Postoperative Cognitive Function and Cerebral Oxygen Metabolism in Elderly Patients with Spinal Surgery

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SUMMARY

Background: To investigate the effect of edaravone on the postoperative cognitive function and cerebral oxygen metabolism in elderly patients with spinal surgery.

Methods: One hundred and twenty patients undergoing elective thoracolumbar surgery, aged 65–75 years, were randomly divided into two groups: edaravone group (Group E, n = 60) and control group (Group C, n = 60). At 30 minutes before anesthesia, the patients in Group E received 0.5 mg/kg edaravone, while the patients in Group C received the same volume of normal saline. Mini-mental state examination (MMSE) was performed at 1 day before the operation, and 1 day and 4 days after the operation.

Results: A total of 26 patients in both groups had postoperative cognitive dysfunction. Compared with the preoperative MMSE scores, postoperative MMSE scores decreased significantly in both groups (p < 0.05) and the reduction in the 1-day postoperative MMSE scores in Group E was remarkably lower than that in Group C (p < 0.05).

Conclusion: Edaravone can reduce the incidence of early postoperative cognitive dysfunction in elderly patients. The underlying mechanism may be related to improvement of cerebral oxygen metabolism.

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1. Introduction

Postoperative cognitive dysfunction (POCD) is an acute mental disorder syndrome caused by multiple-factor-induced deterioration of neurotransmitter system disorder in elderly people on the basis of central nervous system degeneration. More than 200 years ago, it was first reported that postoperative amnesia symptoms occurred in elderly patients undergoing surgery with general anesthesia. And about 100 years ago, postoperative behavior disorder was first reported. However, the term POCD had just emerged and was clearly defined in recent decades. There are many factors that can cause POCD. It has been reported that postoperative mental disorders are often the combined result of many factors, including advanced age, psychological and environmental factors, type and time of anesthesia, intraoperative hypoxemia and hypotension, hypertension, coronary heart disease, and diabetes. One study also reported that the occurrence of POCD may be associated with cerebral oxygen metabolism. A multicenter study showed that the incidence of POCD in elderly people undergoing non-heart surgery is as high as 25.8% within 1 week. To date, the drugs used for improving cognitive function include cholinomimetics, cholinesterase inhibitors, calcium antagonists, and alkaloids. As a new type of oxygen free radical scavenger, edaravone has good curative effect when it is used clinically for brain protection. In this study, we aimed to explore the effect of edaravone on postoperative cognitive function and cerebral oxygen metabolism in elderly patients who underwent thoracolumbar surgery in our hospital, so as to provide some references for clinical medication.

2. Methods

2.1. Patients

One hundred and twenty elderly patients undergoing elective thoracolumbar surgery with general anesthesia were enrolled in...
this study. The patients were aged 65–75 years, and no consider-
eration was given to their gender. All patients were American
Society of Anesthesiologists Grade I or Grade II, without obvious
abnormal preoperative coagulation and kidney function. Patients
with severe lung disease, hypertension, abnormal blood sugar, or
identified neurological or psychiatric disorders were excluded.
Patients with cognitive dysfunction before surgery were also
excluded by mini-mental state examination (MMSE). This study
was conducted in accordance with the Declaration of Helsinki.
This study was approved by the Ethics Committee in our hospital
and written informed consent from each patient was also
obtained.

2.2. Grouping and treatment

The patients were divided into two groups according to the
random digits table method: edaravone group (Group E, n = 60)
and control group (Group C, n = 60). At 30 minutes before anes-
thesia, the patients in Group E received 0.5 mg/kg edaravone
(Nanjing Simcere Pharmaceutical Co., Ltd., Nanjing, China) by
intravenous drip, while the patients in Group C received the same
volume of normal saline.

2.3. Anesthesia

No premedication was applied to any patient before anesthesia
induction. After the patients were sent into the operating room, a
peripheral venous pathway was opened and intravenously dripped
with lactacidsolution. Under local anesthesia, radial artery
puncture and catheterization were carried out to monitor blood
pressure and collect blood samples for blood gas analysis (GEM
Premier 3000; Instrumentation Laboratory, Bedford, MA, USA).
Electrocardiogram, heart rate, and peripheral capillary oxygen
saturation of the patients were regularly monitored. After intra-
venous injection of 0.4 μg/kg sufentanil, 1–2 mg/kg propofol and
0.5 mg/kg rocuronium, the patients received an oral tracheal can-
nula and mechanical ventilation with an anesthesia machine
(Dräger, Hanseatic City of Lubeck, Germany). The tidal volume was
8–10 mL/kg and inspiratory/expiratory volume was 1:2, with a
ventilatory frequency of 10–12 times per minute. End tidal CO2
tension was maintained between 35 mmHg and 40 mmHg
(1 mmHg = 0.133 kPa). After intubation, retrograde puncture and
catheterization were performed via the right internal jugular vein,
leaving the catheter tip in the bulbar zone of the internal jugular
vein. The tube was sealed with heparin for subsequent blood
collection. Anesthesia was maintained with a trace pump at a speed
of 4–6 mg/kg/h of propofol and discontinuous addition of 0.5 mg/
kg atracurium for maintaining muscle relaxation. During the
operation and according to the hemodynamic changes, 0.1–0.2 mg
additional fentanyl could be used. After surgery, the endotracheal
tube was withdrawn when the patient awakened and spontaneous
breathing recovered (tidal volume > 6 mL/kg and respiratory fre-
quency > 10 times/min). The patients were sent to the anesthesia
recovery room with an oxygen mask and routinely monitored.

2.4. MMSE score

MMSE score was measured 1 day before the operation, and
1 day and 4 days after the operation for evaluating the cognitive
function of each patient. Cognitive function was quantitatively
evaluated by asking each patient a series of problems, including the
directive force of the time and place, attention, calculation ability,
short-term review of words, immediate memory, and ability to
copy a graph. POCD was defined as postoperative MMSE score
being reduced by 2 points as compared with the preoperative MMSE
score. The highest MMSE score was 30 points, and > 27 points was
regarded as normal.

2.5. Blood gas analysis

Blood samples were collected synchronously from the radial
artery and the bulbar zone of the internal jugular vein immediately
after anesthesia induction (T0), 1 hour after anesthesia induction
(T1), and immediately after the operation (T2) for blood gas analysis.
The speed of blood withdrawal from the internal jugular vein was
about 1 mL/min. Arterial oxygen content (CaO2), internal jugular
vein oxygen content (CjvO2), arteriovenous oxygen content differ-
ence (Da-jvO2), and cerebral extraction of oxygen (CERO2) were
calculated according to the following formula:

\[
\text{CaO}_2 = 1.34 \times \text{Hb} \times \text{SaO}_2 + 0.0031 \times \text{PaO}_2; \quad (1)
\]

\[
\text{CjvO}_2 = 1.34 \times \text{Hb} \times \text{SjvO}_2 + 0.0031 \times \text{PjvO}_2; \quad (2)
\]

\[
\text{Ca} - \text{jvO}_2 = \text{CaO}_2 - \text{CjvO}_2; \quad (3)
\]

\[
\text{CERO}_2 = \text{Da} - \text{jvO}_2 / \text{CaO}_2 \times 100%. \quad (4)
\]

where Hb = hemoglobin; SaO2 = arterial oxygen saturation;
SjvO2 = internal jugular venous oxygen saturation; PaO2 = arterial
oxygen partial pressure; and PjvO2 = internal jugular venous blood
oxygen partial pressure.

2.6. Statistical analysis

SPSS version 15.0 statistical software (SPSS Inc., Chicago, IL, USA)
was used to process the data in this study. Measurement data were
shown as mean ± standard deviation. One-factor analysis of vari-
ance was used to compare the data among the groups and unitizing
t test was performed for comparison between two groups.
Enumeration data were compared using the χ² test. A p value < 0.05
was considered to be statistically significant.

3. Results

3.1. General data

The age, gender, weight, American Society of Anesthesiologists
grade, anesthesia time, CaO2, red blood cell count, and hemoglobin
did not differ significantly between the edaravone group and con-
trol group (p > 0.05, Table 1).

3.2. MMSE scores

Compared with the preoperative MMSE scores, the MMSE
scores in both groups were significantly reduced at 1 day after
the operation (p < 0.05). Additionally, the reduction of MMSE scores in
Group E was significantly lower than that in Group C (p < 0.05,
Table 2).

3.3. Incidence of POCD

A total of 26 cases of POCD occurred at 1 day after the operation,
including 10 in Group E (16.7%) and 16 in Group C (26.7%), showing
a significant difference between the two groups (p < 0.05).
Data for 120 patients are shown as mean ± standard deviation. American Society of Anesthesiologists; CaO2 — arterial oxygen content; F — female; M — male; RBC — red blood cell count.

Table 1
Comparison of general data between the two groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Age (y)</th>
<th>Weight (kg)</th>
<th>Gender (M/F)</th>
<th>ASA grade (I/II)</th>
<th>Anesthesia time (min)</th>
<th>CaO2 (mL/L)</th>
<th>RBC (10^12/L)</th>
<th>Hemoglobin (g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group E</td>
<td>66.2 ± 2.7</td>
<td>65.2 ± 1.8</td>
<td>38/22</td>
<td>36/24</td>
<td>214.2 ± 1.8</td>
<td>164.5 ± 20.2</td>
<td>43.0 ± 0.8</td>
<td>13.7 ± 0.6</td>
</tr>
<tr>
<td>Group C</td>
<td>67.1 ± 3.8</td>
<td>64.5 ± 2.6</td>
<td>36/24</td>
<td>38/22</td>
<td>220.6 ± 2.6</td>
<td>165.3 ± 21.3</td>
<td>42.0 ± 0.9</td>
<td>12.5 ± 0.8</td>
</tr>
</tbody>
</table>

Data for 120 patients shown as mean ± standard deviation.

ASA — American Society of Anesthesiologists; CaO2 — arterial oxygen content; F — female; M — male; RBC — red blood cell count.

Table 2
Comparison of MMSE scores between the two groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>1d before operation</th>
<th>1d after operation</th>
<th>4d after operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group E</td>
<td>28.8 ± 1.6</td>
<td>23.7 ± 3.6(^{a, b})</td>
<td>28.2 ± 1.6</td>
</tr>
<tr>
<td>Group C</td>
<td>28.3 ± 2.2</td>
<td>21.3 ± 1.4(^{a})</td>
<td>28.1 ± 2.3</td>
</tr>
</tbody>
</table>

Data for 120 patients shown as mean ± standard deviation.

\(^{a}\) \(p < 0.05\) versus 1d before operation.
\(^{b}\) \(p < 0.05\) versus Group C.

3.4. Cerebral oxygen metabolism index

At the time point of T1 and T2, Da-jvO2 and CERO2 in Group E were significantly lower than those at T0 and those in Group C (\(p < 0.05\), Table 3).

4. Discussion

POCD is a common central nervous system complication of surgery with anesthesia, which is likely to occur in patients aged > 65 years, and it is characterized by disorders of memory, abstract thinking, and directive ability. Meanwhile, it is accompanied by the loss of social activities, namely, changes of personality, social abilities, and skills\(^{11}\). A multicenter study shows that the incidence of POCD in elderly patients undergoing non-heart surgery was 25.8% within 1 week after the operation\(^{11}\). However, to date, the cause of POCD is still unclear. Some reports point out that general anesthetics, hypoxemia, hyperlipidemia, and low blood pressure are the risk factors for POCD. Moreover, there are also some reports suggesting that advanced age, long anesthesia time, and low education level are risk factors for early POCD. However, only advanced age is a risk factor for long-term POCD\(^{11, 14}\). Recently, a large number of studies have suggested that cerebral oxygen metabolism disorder is one of the main reasons for POCD.

MMSE score is one of the most influential cognitive impairment screening tools, which is suitable for evaluating the cognitive dysfunction of aging. Although it is widely recognized that elderly people are prone to POCD, the duration of the condition varies. Some reports show that POCD tends to occur at 1–3 days postoperatively\(^{15}\). In the present study, at 1 day after the operation, the MMSE scores in both groups decreased significantly as compared with those before the operation (\(p < 0.05\)). In addition, after treatment with edaravone, the MMSE score of the patients was reduced less significantly than in Group C, suggesting that POCD in the elderly patients was improved. There was no significant difference between the two groups in MMSE scores at 4 days after the operation. This may be related to the duration, different methods of anesthesia, and the anesthetics\(^{16}\). Simultaneously, the reason may be that the influence of anesthesia on cognitive function had disappeared. Edaravone is used temporarily during the operation, and the protective effect on the brain disappeared after 4 days, therefore, there was no significant difference between the two groups.

As the first free radical scavenger to be recognized, edaravone has strong inhibitory effects on free radical damage. It acts by removing reactive oxygen molecules in the body and reducing brain edema, so as to inhibit late-onset neural cell death, thereby protecting the brain\(^{11}\). However, whether it can prevent POCD in elderly patients has not been reported yet. One study on the effect of edaravone on the behavior of rats with vascular cognitive dysfunction has shown that edaravone can improve the memory, ability to learn, and behavior by inhibiting the inflammatory reaction and improving vascular repair\(^{17, 18}\). Our results suggested that perioperative application of edaravone can reduce POCD in elderly patients after surgery with general anesthesia.

The central nervous system is one of the most sensitive organs to ischemia and hypoxia. The oxygen supply and oxygen demand of the brain tissue are two important indicators reflecting oxygen metabolism in brain tissue. Blood in the internal jugular vein bulbar zone is the backflow directly from the brain, which is often clinically used to substitute the cerebral venous blood for measuring its SjvO2\(^{18}\). Combined with Da-jvO2 and CERO2, it can reflect the balance of the cerebral oxygen supply and demand. The reduction of Da-jvO2 and CERO2 suggests that the oxygen consumption of brain tissue decreases and the oxygen supply is sufficient, while a rise of Da-jvO2 and CERO2 indicates the relative increase of cerebral oxygen consumption and the inadequate oxygen supply in brain tissue. Zhang et al\(^{19}\) reported that insufficiency of cerebral oxygen supply can lead to excess production of lactic acid in brain tissue, which increases the incidence of POCD. Various surgical procedures

Table 3
Changes in cerebral oxygen metabolism index.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Groups</th>
<th>No. of cases</th>
<th>(T_0)</th>
<th>(T_1)</th>
<th>(T_2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CaO2 (mL/L)</td>
<td>Group E</td>
<td>60</td>
<td>164.5 ± 20.2</td>
<td>163.5 ± 19.7</td>
<td>165.5 ± 20.1</td>
</tr>
<tr>
<td></td>
<td>Group C</td>
<td>60</td>
<td>165.3 ± 21.3</td>
<td>166.5 ± 20.2</td>
<td>166.3 ± 18.5</td>
</tr>
<tr>
<td>CvjO2 (mL/L)</td>
<td>Group E</td>
<td>60</td>
<td>111.3 ± 17.9</td>
<td>121.7 ± 15.0</td>
<td>122.1 ± 16.5</td>
</tr>
<tr>
<td></td>
<td>Group C</td>
<td>60</td>
<td>113.5 ± 17.5</td>
<td>115.7 ± 17.5</td>
<td>114.4 ± 15.2</td>
</tr>
<tr>
<td>Da-jvO2 (mL/L)</td>
<td>Group E</td>
<td>60</td>
<td>50.2 ± 14.3</td>
<td>40.3 ± 13.5(^{a, b})</td>
<td>41.1 ± 12.5(^{a, b})</td>
</tr>
<tr>
<td></td>
<td>Group C</td>
<td>60</td>
<td>50.8 ± 15.2</td>
<td>52.7 ± 13.7</td>
<td>51.8 ± 11.8</td>
</tr>
<tr>
<td>CERO2 (%)</td>
<td>Group E</td>
<td>60</td>
<td>30.2 ± 5.5</td>
<td>25.2 ± 5.2(^{a, b})</td>
<td>25.3 ± 6.3(^{a, b})</td>
</tr>
<tr>
<td></td>
<td>Group C</td>
<td>60</td>
<td>31.1 ± 6.2</td>
<td>30.7 ± 6.8</td>
<td>31.7 ± 6.1</td>
</tr>
</tbody>
</table>

Data shown as mean ± standard deviation.

CaO2 — arterial oxygen content; CERO2 — cerebral extraction of oxygen; CvjO2 — internal jugular vein oxygen content; Da-jvO2 — arteriovenous oxygen content difference; \(T_0\) — immediately after anesthesia induction; \(T_1\) — 1 hour after anesthesia induction; \(T_2\) — immediately after the operation.

\(^{a}\) \(p < 0.05\) versus \(T_0\).
\(^{b}\) \(p < 0.05\) versus Group C.
should be combined with coronary artery bypass grafting for a smoother, less complicated recovery. In this study, we found that the Da-VO2 and CERO2 in Group E were reduced at 1 hour after anesthesia induction and at the end of the surgery, suggesting that edaravone can reduce cerebral oxygen consumption and improve cerebral oxygen supply, with the extensive application of anesthetics, and thereby reduce the occurrence of POCD.

In conclusion, edaravone can improve early POCD in elderly patients undergoing spinal surgery. It reduces the occurrence of POCD, probably by reducing cerebral oxygen consumption and improving cerebral oxygen supply. The underlying mechanism needs further exploration.

References