The clinical effect of vagus nerve stimulation in the treatment of patients with a minimally conscious state

Xun-Jie Xiang  
Neurosurgery Department, Guangxi Jiangbin Hospital, Nanning 530021, Guangxi, China

Liu-Zhong Sun  
Neurosurgery Department, Guangxi Jiangbin Hospital, Nanning 530021, Guangxi, China

Cai-Bang Xu  
Neurosurgery Department, Guangxi Jiangbin Hospital, Nanning 530021, Guangxi, China

Yong Xie  
Neurosurgery Department, Guangxi Jiangbin Hospital, Nanning 530021, Guangxi, China

Ming-Yan Pan  
Neurosurgery Department, Guangxi Jiangbin Hospital, Nanning 530021, Guangxi, China

See next page for additional authors

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Authors
Xun-Jie Xiang, Liu-Zhong Sun, Cai-Bang Xu, Yong Xie, Ming-Yan Pan, Jiang Ran, Yang Hu, Bang-Xie Nong, Qu Shen, Hua Huang, Sheng-Hui Huang, and Yan-Zhong Yu
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Xun-Jie Xiang (✉), Liu-Zhong Sun, Cai-Bang Xu, Yong Xie, Ming-Yan Pan, Jiang Ran, Yang Hu, Bang-Xie Nong, Qu Shen, Hua Huang, Sheng-Hui Huang, Yan-Zhong Yu

Neurosurgery Department, Guangxi Jiangbin Hospital, Nanning 530021, Guangxi, China

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disorders of consciousness; vegetative state; minimally conscious state; vagus nerve stimulation

ABSTRACT
Objective: Vagus nerve stimulation (VNS) has recently been used in neurorehabilitation and the recovery of consciousness based on its effects on cortical plasticity. The aim of this study was to examine the therapeutic effects of VNS on patients with a minimally conscious state (MCS).

Methods: All patients included in the study were assessed more than 5 months after injury and were receiving regular rehabilitation at our hospital from August 2018 to October 2019. Ten patients diagnosed with MCS by Coma Recovery Scale-Revised (CRS-R) test who underwent VNS surgery were enrolled. The scores on CRS-R evaluation at baseline (before VNS implantation) and 1, 3, and 6 months after VNS treatment were recorded. The stimulation parameters were chosen according to a previous study. All clinical rehabilitation protocols remained unchanged during the study. Furthermore, safety was assessed by analyzing treatment-emergent adverse events (TEAEs).

Results: No significant improvement in the total CRS-R scores at the end of the 1-month follow-up was observed (p > 0.05). After 3 months of stimulation, a significant difference (p = 0.0078) was observed in the total CRS-R scores compared with the baseline. After 6 months of VNS treatment, CRS-R assessments showed a continuous significant improvement (p = 0.0039); one patient emerged from the MCS and recovered functional communication and object use. Interestingly, one item of CRS-R scores on visual domain was sensitive to VNS treatment (p = 0.0039). Furthermore, no serious adverse event occurred throughout the study.

Conclusion: This exploratory study provides preliminary evidence suggesting that VNS is a safe and effective tool for consciousness recovery in patients with MCS.

Corresponding author: Xun-Jie Xiang, E-mail: xxjsun@163.com
1 Introduction

Disorders of consciousness (DOC) are one of many neurological disorders caused by severe brain injury, including coma, unresponsive wakefulness syndrome (UWS, or vegetative state), and minimally conscious state (MCS) [1, 2]. MCS is characterized by severe dysfunctions in consciousness, and unlike vegetative state (VS), patients with MCS have a clear and repeated awareness of themselves or their surrounding environment [3]. Once patients recover functional communication or object use, they emerge from the MCS [4]. Due to the impairments of various functions in the brain, such as UWS, MCS can be temporary or permanent. Therefore, it is very difficult to distinguish it from the VS clinically, and the probability of misdiagnosis is very high [5]. Fortunately, modern neuroimaging and electrophysiological studies have found that MCS and VS are significantly different with regard to residual brain function, sensitivity to stimulations, and medical prognosis [2, 4, 6]. Recent clinical evidence demonstrates that unlike in VS/UWS, disrupted cortical networks contribute overly to the symptoms expressed in MCS [7–9]. In other terms, compared with VS/UWS, MCS can be reinterpreted as a cortically mediated state (CMS) and is more likely to evolve to the recovery of consciousness [10].

However, no curative strategy for patients with DOC has been established to date. The main stream of therapeutic options performed in these patients has focused on accelerating the clinical recovery through pharmacological interventions [11–13], sensory stimulation [14–16], or neuromodulatory brain stimulation [17–21]. For the treatment of MCS, many traditional methods result in poor outcomes. In recent years, novel neuromodulatory treatments, such as deep brain stimulation (DBS), spinal cord stimulation (SCS), transcranial magnetic stimulation, and VNS [22–25], have been widely applied in restoring consciousness and cognitive function. But these emerging methods are still under investigation in order to verify their efficiency and safety. VNS has been proven as a promising neuromodulatory electrocortical in the treatment of medically intractable epilepsy [26] and drug-resistant depression [27] and holds potential for the management of a wide range of neuropsychiatric disorders by reversing the pathological brain plasticity [28, 29]. The implications of the connectomics and the introduction of large-scale remodeling of brain networks has helped elucidate the underlying neurophysiology of VNS [30]. A lot of evidence has been reported that VNS paired with sensory, motor, or cognitive training can generate highly specific, long-lasting, and therapeutic neural plasticity that results in relevant cognitive and behavioral changes [29, 31]. The proposed mechanisms involve a range of influences on different levels in the nervous system, including the alterations of neurotransmitters, synaptic connections, neuro-glial communications, anti-inflammatory effects, as well as neurogenesis [29, 30, 32, 33]. VNS can influence important components of the limbic system via the anatomical projection pathways, such as the amygdala, hippocampus, thalamus, hypothalamus, and neocortex via recruiting monoaminergic signalings, which include glutamate (Glu), serotonin (5-HT), dopamine (DA), and norepinephrine (NE) [34]. VNS can also directly lead to the rapid and transient enhancement of the thalamic information transmission [35] and the activation of brain regions which covers more than 76% of the brain volume [36]. Thus, VNS-activated brain regions were involved in the dominant corticothalamic circuits in which
the disconnections in the cortico–cortical and thalamo–cortical pathways mediated the neural mechanisms of the impaired consciousness [4, 21]. Such finding implies that VNS could be an effective tool for patients with MCS. It not only helps in the emergence from MCS but also in boosting the cognitive and locomotive rehabilitation, because most of these patients still have severe cognitive and motor impairments [37].

Vagus nerve stimulation (VNS) has recently been applied in neurorehabilitation based on its effects on reversing pathological cortical circuits by targeting the vagus afferent network [32, 33, 38, 39]. Clinical evidences suggest that VNS reduces daytime sleepiness, promotes vigilance in refractory epilepsy, and maintains the awakening state of epilepsy patients with impaired consciousness [40–42]. Three studies that used VNS have shown promising results in increasing the consciousness level in patients with DOC after severe traumatic brain injury [21, 43, 44]. Moreover, data from animal studies also suggest that VNS may have beneficial effects on the recovery of consciousness and cognitive function following experimental TBI (traumatic brain injury) [45]. Such evidences further suggest the activation of the task-related brain region and regulation of neuroplasticity in the cortex could be facilitated by VNS in patients with MCS. However, the therapeutic effect of VNS on patients with MCS has not been systematically investigated.

In this study, we hypothesized that VNS treatment paired with regular neurorehabilitation would improve the recovery of consciousness in patients with MCS. Ten patients diagnosed with MCS using the Coma Recovery Scale-Revised (CRS-R) test who underwent VNS surgery were enrolled to determine the therapeutic effects of VNS on DOC.

### 2 Materials and methods

#### 2.1 Participants

Ten patients (5 males and 5 females, mean age 43.90 ± 15.79 years) with MCS who underwent VNS implantation in our hospital from August 2018 to October 2019 were enrolled. The time since injury was on an average of 7.16 ± 2.12 months and ranged from 5 months to 11.5 months (Table 1). We enrolled patients who met the following inclusion criteria: (1) regular and systematic neurorehabilitation for more than 5 months after brain injury, with age ≥ 18 years old; (2) at least one neurological examination and consistent with MCS defined by the CRS-R

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Causes</th>
<th>Course (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>24</td>
<td>Traumatic brain injury</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>61</td>
<td>Traumatic brain injury</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>66</td>
<td>Cerebral infarction, hemorrhage after thrombolysis</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>39</td>
<td>Traumatic brain injury</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>55</td>
<td>Cerebral hemorrhage</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>Female</td>
<td>47</td>
<td>Traumatic brain injury</td>
<td>6.5</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>51</td>
<td>Cerebral hemorrhage</td>
<td>8</td>
</tr>
<tr>
<td>8</td>
<td>Female</td>
<td>39</td>
<td>Cerebral hemorrhage</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>Male</td>
<td>48</td>
<td>Cerebral hemorrhage</td>
<td>6.6</td>
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<tr>
<td>10</td>
<td>Male</td>
<td>29</td>
<td>Hypoxic–ischemic encephalopathy</td>
<td>11.5</td>
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</tbody>
</table>
test; and (3) informed written consent for the patients’ participation of the study given by their legal surrogates. The exclusion criteria included the following: (1) patients in a vegetative state; (2) with an injury course less than 5 months; (3) aged < 18 years old; (4) patients’ legal surrogates disagree with the VNS treatment; (5) patients who were in poor condition (dysfunction of important organs or obvious infections) and cannot support the operation. The Ethics Committee of the Jiangbin Hospital approved the whole protocol and procedure in this study.

2.2 VNS implantation

Before the VNS implantation, all the patients were assigned to undertake the following preoperative examinations: (1) routine preoperative examination (chest radiograph, electrocardiogram, and laboratory test) to understand the function of each important organ and surgery tolerance; (2) preoperative skull computed tomography (CT) and/or magnetic resonance imaging (MRI) examination to understand the situation of intracranial injury; and (3) electroencephalogram (EEG).

Following the clinical screening, the patients were formally included in the study to receive the VNS System (G112, PINS Medical, Ltd., Beijing, China) implantation performed as VNS for medically refractory epilepsy.

2.3 Adjustment of VNS parameters

The device was switched on about 2–4 weeks after the implantation at an initial current 0.1–0.3 mA with a pulse frequency of 20–30 Hz and a pulse duration of 250 or 500 µs. The protocol followed the standard stimulation cycles, previously used for medically refractory epilepsy treatment, consisting of 30 seconds of stimulation interleaved by 5 minutes of rest. During the first month and a half, the current amplitude was increased by 0.2–0.3 mA every 1–2 weeks until the maximal current of 1.5 mA was reached. Afterwards, the parameter adjustment was based on the patient’s tolerance and clinical conditions, but the maximum current is less than 3.5 mA (Suppl. 1). When the VNS was reaching a satisfactory efficacy without obvious adverse events, the stimulation parameters were kept unvaried throughout the following months.

2.4 Behavioral assessment

The CRS-R test was used to assess the clinical state of the patient along with the whole protocol of the VNS treatment. During the baseline and VNS sessions (1 month, 3 months, and 6 months after implantation), a CRS-R evaluation was performed by expert clinicians. Emergence from a minimally conscious state: when patients were able to functionally communicate or adequately use two different objects, it was considered an emergence from the MCS. Significant improvement: at least 4 points in the total CRS-R scores were increased. VNS-responsive patients: CRS-R score increased by ≥ 2 points. Unresponsive patients: the total CRS-R scores increased by ≤ 1. Safety was primarily assessed in the analysis of the treatment-emergent adverse events (TEAEs).

2.5 Statistical analysis

Descriptive analysis was conducted to summarize the patient characteristics. A Wilcoxon matched-pairs signed rank test was used for one sample comparison of the abnormally distributed variables. A p-value < 0.05 was considered a statistically significant difference. All statistical analyses were performed in GraphPad Prism v8.0 (GraphPad; LaJolla, CA).
3 Results

10 patients (5 males and 5 females, mean age 43.90 ± 15.79 years) with MCS who underwent VNS implantation were enrolled in this study. The time since injury was on an average of 7.16 ± 2.12 months and ranged from 5 months to 11.5 months. The causes of MCS included four cases of traumatic brain injury, five cases of cerebral hemorrhage, and one case of ischemic hypoxic encephalopathy (Table 1). All the patients completed the 6-month follow-up. No severe adverse events related to the VNS implantation or programming were recorded during the therapeutic protocol.

Moreover, no significant improvement was observed in the total CRS-R scores at the end of the 1-month follow-up versus baseline (p > 0.05) (Table 2 and 3). After 3 months of stimulation, a significant difference in the total CRS-R scores compared with that at baseline (p = 0.0078), 3/10 (30.0%) showed a significant improvement; 2/10 (20.0%) were VNS-responders, and 5/10 cases (50.0%) were unresponsive to the VNS treatment. Specifically, one CRS-R subscale on the visual function was more sensitive to VNS (p = 0.0156) (Table 4). Surprisingly, CRS-R assessments showed a continuous significant improvement (p = 0.0039) after 6 months of stimulation. Similarly, visual function significantly improved compared with that at baseline (p = 0.0078). 1/10 (10.0%) has emerged from the minimally conscious state and recovered functional communication and object use. 2/10 (20.0%) showed a significant improvement, 3/10 (30.0%) were responsive, and 5/10 (50.0%) were unresponsive to VNS. However, no difference was observed in the total and subscale CRS-R assessments in a comparison between the 6- and 3-month follow-ups (p > 0.05) (Table 2 and 4).

Table 2 The total CRS-R scores of MCS patients at baseline and 1 month, 3 months, 6 months after VNS.

<table>
<thead>
<tr>
<th>Case</th>
<th>Baseline</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
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</thead>
<tbody>
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<td>10</td>
<td>11</td>
<td>12</td>
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<td>2</td>
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<td>10</td>
<td>11</td>
<td>11</td>
</tr>
</tbody>
</table>

Table 3 Statistical analysis (p-value) of behavioral assessment by CRS-R test.

<table>
<thead>
<tr>
<th></th>
<th>1M vs. baseline</th>
<th>3M vs. baseline</th>
<th>6M vs. baseline</th>
<th>1M vs. 3M</th>
<th>1M vs. 6M</th>
<th>3M vs. 6M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CRS-R score</td>
<td>&gt; 0.05</td>
<td>0.0078</td>
<td>0.0039</td>
<td>0.0156</td>
<td>0.0078</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Auditory function</td>
<td>/</td>
<td>&gt; 0.05</td>
<td>&gt; 0.05</td>
<td>&gt; 0.05</td>
<td>&gt; 0.05</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Visual function</td>
<td>&gt; 0.05</td>
<td>0.0156</td>
<td>0.0078</td>
<td>0.0313</td>
<td>0.0156</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Motor function</td>
<td>/</td>
<td>&gt; 0.05</td>
<td>&gt; 0.05</td>
<td>&gt; 0.05</td>
<td>&gt; 0.05</td>
<td>&gt; 0.05</td>
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<tr>
<td>Oromotor/verbal function</td>
<td>&gt; 0.05</td>
<td>&gt; 0.05</td>
<td>&gt; 0.05</td>
<td>&gt; 0.05</td>
<td>&gt; 0.05</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Communication</td>
<td>/</td>
<td>/</td>
<td>&gt; 0.05</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Arousal</td>
<td>&gt; 0.05</td>
<td>&gt; 0.05</td>
<td>&gt; 0.05</td>
<td>&gt; 0.05</td>
<td>&gt; 0.05</td>
<td>/</td>
</tr>
</tbody>
</table>

Neither of the 10 patients had complications such as nerve damage, arrhythmia, or infection of the surgical mouth. /, no difference and cannot be analyzed. M, month(s).
Table 4  The specific CRS-R subscales of each patient during follow-up.

<table>
<thead>
<tr>
<th>Case</th>
<th>Auditory function scale Base-line 1M 3M 6M</th>
<th>Visual function scale Base-line 1M 3M 6M</th>
<th>Motor function scale Base-line 1M 3M 6M</th>
<th>Oromotor/verbal function scale Base-line 1M 3M 6M</th>
<th>Communication scale Base-line 1M 3M 6M</th>
<th>Arousal scale Base-line 1M 3M 6M</th>
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<td>2 2 2 2</td>
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<td>1 1 1 1</td>
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<td>2 2 2 2</td>
<td>1 2 2 2</td>
<td>1 2 2 2</td>
<td>1 1 1 1</td>
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<td>1 2 2 2</td>
<td>1 2 2 2</td>
<td>1 1 1 1</td>
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<td>2 2 2 2</td>
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<td>1 2 3 4</td>
<td>1 1 1 1</td>
<td>2 2 3 4</td>
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<td>2 2 3 3</td>
<td>1 2 3 3</td>
<td>1 2 3 3</td>
<td>1 1 1 1</td>
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<td>1 1 1 1</td>
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<tr>
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<td>2 2 3 3</td>
<td>1 2 3 3</td>
<td>1 2 3 3</td>
<td>1 1 1 1</td>
<td>2 2 3 3</td>
</tr>
<tr>
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<td>2 2 2 2</td>
<td>1 2 2 2</td>
<td>1 2 2 2</td>
<td>1 1 1 1</td>
<td>2 2 2 2</td>
</tr>
</tbody>
</table>

M, month(s).

4 Discussion

To the best of our knowledge, this is the largest single-center prospective study assessing the overall efficacy, safety, and tolerability of the surgically implanted VNS in MCS patients so far. In this study, the CRS-R test was used to evaluate the clinical states of 10 patients with MCS treated with VNS. No significant improvement was observed in total CRS-R scores at the end of the 1-month follow-up. The outcomes of the VNS treatment need time to emerge as well-known, just like its cumulative benefits observed in patients with epilepsy or depression who underwent the VNS implantation. The nature of experience-dependent neural plasticity explains the need for intensive and repetitive stimulation over time for a therapeutic procedure of rehabilitation in humans with brain damage [26]. After 3 months of stimulation, a significant difference was observed in the total CRS-R scores compared with that at baseline: 3/10 (30.0%) showed a significant improvement at 3 months after VNS treatment, and 2/10 (20.0%) were responsive. After 6 months of VNS treatment, CRS-R assessments showed a continuous significant improvement: 1 patient has emerged from the MCS, 2/10 (20.0%) showed significant improvement, and 2/10 (20.0%) were responsive. Six months was proven enough to observe the physical and neurological changes based on the CRS-R results after the VNS treatment [21]. Interestingly, one CRS-R subscale item, visual item, was sensitive to the VNS treatment. Moreover, this result is consistent with the previous study in which scores on the CRS-R test improved, mostly in the visual domain, as stimulation increased during the VNS treatment [21]. Animal studies also revealed that VNS had transitory effects on the neural activity of the primary visual pathway structures and interferes with the development and establishment of visual habituation [46]. The pattern of changes described here could be explained in the literature regarding the VNS-directed auditory map plasticity mediated by neurotransmitters to treat tinnitus [47] and the enhancement of motor cortex plasticity in stroke recovery [32, 33]. The above results show that VNS works slowly, but continuously, in patients with MCS. This phenomenon may be related to the increasing large-scale functional
connectivity and reversing pathological brain plasticity because of the long-lasting effects of VNS, and persistent clinical changes may require a continuous application of the neurophysiological technique to be detected.

The curative effects of tVNS (transcutaneous vagus nerve stimulation) have been preliminary verified in patients with a persistent impairment of consciousness [25, 44]. However, it is difficult to directly compare the therapeutic effect between tVNS and VNS, because of the different stimulation methods, efficiency, and duration. Meanwhile, the application of tVNS is still under initiatory investigation and needs more controlled studies with large samples to assess its long-term effects and safety, but the advantage of tVNS is that patients with DOC can receive therapy in an noninvasive manner and at a relative low cost.

It has been agreed that DOC may involve impairments in the long-range cortico-cortical and thalamo-cortical circuits, and the neural signature of spontaneous recovery is linked to increased thalamo-cortical activity and improved fronto-parietal functional connectivity [48]. It is known that vagal fibers first project to the nucleus tractus solitarius (NTS), which serves as a major relay center of vagal afferent pathways and subsequent travels to other brainstem nuclei important in modulating the activity of subcortical and cortical circuitry [30]. Therefore, more neurophysiological and neuroimaging data are required to clinically evaluate the alterations of preserved brain connectivity and cortical plastic properties in patients with MCS after VNS. At the same time, this is the most common deficiency of our research, and we will improve the neurophysiological and imaging tools to make a comprehensive study. In addition, VNS may protect the internal organs of the body by triggering inflammation reflex and enhancing metabolic activity [31]. Thus, more physiological evaluation, such as heart rate, respiration function, body motility, and inflammation level, should be considered in future studies. Our results suggested that the use of VNS was feasible and safe in patients with DOC and that it may improve behavioral responses when applied to patients with MCS. It should be emphasized that VNS may continuously boost cognitive and locomotive rehabilitation even after emergence from MCS, considering that VNS paired with a specific stimulus can reverse the pathological neuronal circuits [32, 38, 39], but this requires a longer follow-up period and more systematic research to confirm.

Although some improvements were observed in our study, these results should be interpreted with caution considering the lack of a control group, small sample size, and inadequate follow-up time.

5 Conclusion

This exploratory study provides a preliminary evidence suggesting that VNS could be a safe and effective tool to facilitate consciousness recovery in patients with MCS. It appears that the recovery of visual perception may be more likely to benefit from VNS treatment. Longer treatment periods and more controlled clinical trials are required to verify the effect of VNS in patients with DOC, especially considering that this technique seems to be safe and well-tolerated in this population.

Conflict of interests

All contributing authors reported no conflicts of interests in this work.
References


Xun-Jie Xiang, B.S., Neurosurgery Department of Guangxi Jiangbin Hospital, Guangxi, China. He focuses on the research and treatment of functional neurosurgical diseases and traumatic brain diseases. E-mail: xxjsun@163.com

Liu-Zhong Sun, B.S., Neurosurgery Department of Guangxi Jiangbin Hospital. He focuses on the research and treatment of functional neurosurgical diseases and traumatic brain diseases. E-mail: 247984643@qq.com

Cai-Bang Xu, B.S., Neurosurgery Department of Guangxi Jiangbin Hospital. He specializes in the interventional therapy of cerebrovascular diseases, treatment of severe extracranial injury and nerve regulation.

Yong Xie, B.S., Neurosurgery Department of Guangxi Jiangbin Hospital. He specializes in the disease vascular disease research, and is good at nerve interventional therapy. E-mail: 65045725@qq.com
Ming-Yan Pang, M.M., Neurosurgery Department of Guangxi Jiangbin Hospital. He focuses on the research and treatment of functional neurosurgical diseases. E-mail: a_sol@163.com

Jiang Ran, B.S., Neurosurgery Department of Guangxi Jiangbin Hospital. He focuses on the research and treatment of functional neurosurgical diseases and traumatic brain diseases. E-mail: 446220945@qq.com

Yang Hu, M.S., Neurosurgery Department of Guangxi Jiangbin Hospital. His research focuses on cerebrovascular disease, and he is good at neurointerventional therapy. E-mail: 18860054785@163.com

Bang-Xie Nong, B.S., Neurosurgery Department of Guangxi Jiangbin Hospital. His research focuses on cerebrovascular disease, and he is good at neurointerventional therapy. E-mail: 286644549@qq.com

Qu Shen, B.S., Neurosurgery Department of Guangxi Jiangbin Hospital. He focuses on the research and treatment of cerebrovascular disease, and is good at interventional treatment of cerebrovascular disease. E-mail: 1019071818@qq.com
Hua Huang, B.S., Neurosurgery Department of Guangxi Jiangbin Hospital. His research focuses on cerebrovascular disease, and he is good at neurointerventional therapy. E-mail: 56203831@qq.com

Sheng-Hui Huang, B.S., Neurosurgery Department of Guangxi Jiangbin Hospital. He focus on the research and treatment of cerebrovascular disease and craniocerebral injury. E-mail: 974236096@qq.com

Yan-Zhong Yu, Bachelor of Neurosurgery, Guangxi Jiangbin Hospital. He focuses on the research and treatment of cerebrovascular disease and brain injury. E-mail: 22739831@qq.com