Neurology Asia 2022; 27(3) : 753 – 761

Efficacy of high-cervical spinal cord stimulation in vegetative patients and its effect on blood flow

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Abstract

To investigate the efficacy of high-cervical spinal cord stimulation in vegetative patients and its effect on blood flow. Sixty patients with persistent vegetative state were assigned in a control group (n=30) for routine coma arousal program and a treatment group (n=30) for high-cervical spinal cord stimulation besides routine coma arousal program using a random number table method. The number of patients out from vegetative state, consciousness (Coma Recovery Scale-revised), electroencephalogram, brainstem auditory evoked potential, somatosensory evoked potential and cerebral blood flow were observed before and post treatment. One patient in the control group while seven patients in the treatment group were out from vegetative state 6 months after treatment (P<0.05). Post-treatment Coma Recovery Scale-Revised scores increased in both groups of patients (9.23±2.78 *vs* 4.43±1.06 and 7.12±2.91 *vs* 4.51±1.16, P<0.001), with a more evident increase in the treatment group than in the control group (9.23±2.78 *vs* 7.12±2.91, P<0.01). Electroencephalogram, brainstem auditory evoked potential and somatosensory evoked potential enhanced post treatment (all P<0.01), with greater improvements in the treatment group (all P<0.01). Cerebral blood flow rose in both groups post treatment (56.32±5.88 *vs* 44.22±5.21 and 51.12±5.56 *vs* 44.99±5.32, P<0.001), with a more distinct increase in the treatment group than in the control group (56.32±5.88 *vs* 51.12±5.56, P<0.001). High-cervical spinal cord stimulation for patients with persistent vegetative state can promote the recovery of consciousness, enhance neuroelectrophysiological activity and improve cerebral blood flow. However, more clinical studies are needed to confirm its efficacy.

Keywords: High-cervical spinal cord stimulation, vegetative state, cerebral blood flow, clinical curative effect

INTRODUCTION

The survival rate of patients with severe craniocerebral injury has improved substantially after treatment attributing to the constant advances in medical technology, but it is often accompanied by sequelae such as disturbance of consciousness.[1] Generally, patients with mild disturbance of consciousness can recover from a brief coma, but a persistent vegetative state (PVS) is a more severe and enduring disturbance of consciousness.[2,3] Therefore, the key goal to treat PVS patients is to regain consciousness and alleviate the disturbance of consciousness as much as possible.

Although there are many treatment options for the regain of consciousness of PVS patients, the requirements for clinical attention are high, the treatment is difficult, and the effect is not clear. Nor is there any standard treatment scheme for awakening PVS patients.[4,5]

It is shown that the use of spinal cord stimulation (SCS) is conducive to the recovery of consciousness of patients with consciousness disorder.[6] SCS is a treatment that uses electrical impulses to stimulate the nerves of the spinal cord.[7] It was mainly used to treat chronic pain, bladder dysfunction caused by spinal cord injury, lower limb ischemia, tracheal spasm and gastrointestinal dysfunction.[8-10] For PVS patients, the primary injury after brain trauma or cerebral hemorrhage is not irreversible. Improving blood and oxygen supply to the head, improving microcirculation and blocking the secondary nerve injury are the key to neuroprotection regardless of the stage. With the progress of biomaterials and the development of nerve electrophysiology, high cervical spinal cord stimulation (cSCS) has been

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Date of Submission: 10 June 2021; Date of Acceptance: 19 June 2022

https://doi.org/10.54029/2022wsj

observed in clinical studies to stimulate nerves and improve blood supply to the brain, allowing for its application in treating PVS patients. A study included 214 PVS patients who received cSCS has found that 54% of the patients improved their consciousness after treatment.[11] A study in China included 22 patients with severe disturbance of consciousness also confirmed the role played by cSCS in treating PVS patients.[12] However, the clinical application of cSCS is greatly limited due to the difficulty in operation and high cost, as well as the uncertain prognosis. Based on this, this clinical trial enrolled 60 cases of PVS admitted to our hospital to observe the efficacy of cSCS in the treatment of PVS and to provide more clinical reference.

METHODS

Clinical data

PVS patients (n=60) admitted to Guangdong Sanjiu Brain Hospital between June 2020 and April 2021 were assigned to a control group (n=30) for routine coma arousal program and a treatment group (n=30) for cSCS besides routine coma arousal program using a random number table method. The family members of the patients included in this study have signed the consent after the approval of this study from the Ethics Committee of Guangdong Sanjiu Brain Hospital.

Inclusion criteria

(1) All the study patients fulfilled the diagnostic criteria of PVS. The clinical diagnostic criteria of vegetative state in China are as follows: a. Unconscious state with loss of cognitive function and inability to execute instructions; b. Has a sleep-wake cycle; c. Has stable blood pressure and spontaneous breathing rhythm; d. No ability of language expression and understanding; e. Ability to conduct purposeful eye tracking movement; f. Ability to open eyes under stimulation or automatically open eyes; g. Has basically preserved functions of brain stem and hypothalamus. The maintenance of the above state for more than one month is defined as PVS.[13] (2) PVS lasted for more than 6 months. (3) Their age was from 18 to 73 years old.

Exclusion criteria

(1) Patients with hypoxia symptoms that cannot be corrected; (2) Patients with surgery intolerance; (3) Patients with metal implants in the brain; (4) Patients with abnormal coagulation function; (5) Patients who could not receive surgery due to severe cardiopulmonary diseases; (6) Patients with malignancies. (7) Patients who cannot receive treatment continually due to infection and bleeding during surgical treatment.

METHODS

The control group

Patients in this group received routine coma arousal program.[14] See Table 1 for details.

The treatment group

Patients in this group were given cSCS by spinal surgeon in addition to the treatment for the control group. The stimulator was implanted at the 2nd-3rd segments of the cervical spine (Medtronic, USA) for 30 min each time, with the parameters set as follows: amplitude: 0.10-0.45ms, frequency: 35Hz, voltage 2.0-3.0 V. Each stimulation was followed by 1.5h of rest, and the stimulation therapy was repeated 6 times each day (a total of 12h) for 9 consecutive months. The therapeutic effect was followed up 9 months after treatment.

Outcome measures

Vegetative state

The patients' condition after treatment was evaluated by the spine surgeon systematically, and the number of patients who were out of after treatment was recorded.

The state of consciousness of patients was assessed by Coma Recovery Scale-revised (CRS-R)

The CRS-R covers six subscales, including auditory (0-4 points), visual (0-5 points), motor (0-5 points), speech (0-3 points), communication (0-2 points) and arousal (0-3 points), with a total score ranging from 0 to 22. A higher score indicates a better recovery of consciousness.[15] It can be adopted to evaluate the patient's consciousness state.

Electroencephalogram (EEG) before and after treatment

According to Young's classification, EEG is divided into grades I-VI: grade I: Regular δ wave or θ wave records >50% (without θ coma); grade II: Triphasice wave; grade III: Burst-suppression; grade IV: α coma, θ coma or spindle coma

Table 1: Routine coma arousal program

(1) General treatment for PVS	a. Keeping the respiratory tract of patients unobstructed and ensuring oxygen supply;
	b. Providing bedside care and skin care;
	c. Positioning the functional position of limbs to prevent limb contracture, muscle atrophy and disuse syndrome;
	d. Controlling infection;
	e. Providing nutritional support to keep the balance of nutrition, water and electrolyte of patients;
	f. Preventing complications such as epilepsy and deep venous thrombosis of lower limbs.
(2) The Coma arousal program for PVS generally include	a. Passive swallowing function training: patients' swallowing function was trained via oral ice stimulation, passive movement of swallowing organs and swallowing training;
	b. Auditory stimulation: patients' hearing was stimulated by various daily environmental sounds, such as car sounds, water currents, telephones, bell sounds, music familiar to patients, toy sounds, and family sounds;
	c. Visual stimulation: strong and weak light stimulation, family photos and colorful pictures were used to stimulate the visual function of patients;
	d. Taste stimulation: patients' taste was stimulated combined with swallowing function training;
	e. Olfactory stimulation
	f. Various stimuli in daily life, such as calling nursing, caressing, and calling communication were utilized to regain the consciousness of PVS patients.
(3) Exercise therapy for PVS mainly includes	a. Passive range of motion (PROM) training, in which patients' wrist, elbow, shoulder, hip, knee, ankle and other big joints are passively moved in all directions;
	b. Standing training and passive sitting training are performed, so that patients can fully feel the body gravity effect and stimulate the excitability of cortex in feedback.
(4) Acupuncture therapy	Acupuncture-based comprehensive therapy can support vital energy, relax channels and activate collaterals, promote qi and blood circulation, and awake and enlighten the brain. Combined with moxibustion, electroacupuncture stimulation can increase the sensory stimulation and promote the recovery of consciousness of PVS patients.[14]
(5) Neurotrophic drugs	40 mg monosialoteterahexosyl ganglioside was dissolved in 100mL 0.9% normal saline for intravenous drip once daily.

(no response); grade V: Persistent epileptiform activity (not in burst-suppression pattern); grade VI: Generalized suppression.[16]

Measurement of brainstem auditory evoked potential (BAEP) before and after treatment

According to the Greenberg classification, BAEP is divided into grades I-IV: grade I: Basically normal; grade II, Wave I-V are clearly distinguishable, but the latency is prolonged, and the amplitude is decreased; grade III: The latency and amplitude of wave I was normal, and some other waves existed or showed undifferentiated positive phase waves; grade IV: The waveform is difficult to distinguish or only I wave exists.[17]

Somatosensory evoked potential (SEP)

According to the Greenberg classification, SEP is divided into grades I-IV: grade I: Basically normal; grade II: N20 differentiation is fair, the latency is prolonged, and the amplitude is reduced; grade III: N20 is poorly formed, but

identifiable; grade IV: All waves disappear or N20 disappears.[17] The above three indexes can be adopted to effectively evaluate the physiological potential of patients.

Measurement of cerebral blood flow (CBF) by TCD before and after treatment

Pre- and post-treatment mean blood flow velocities (Vm) of the middle cerebral artery were determined.[18]

Statistical analysis

Data analysis was made by SPSS 20.0 statistical software. Continuous variables including CRS-R score and cerebral blood flow were given mean ± standard deviation ($\overline{x}$ ± sd), and those following normal distribution and homogeneity of variance were analyzed by independent sample t test and represented by t. Inter- and intra-group comparisons were performed by independent-sample t test and paired sample t test respectively. Pearson chi-square test was applied to analyze the counting data including EEG, brainstem auditory evoked potential and somatosensory evoked potential there were expressed as χ^2. The ranked data were analyzed by the chi-square test and expressed by chi-square. The significance level was set at P<0.05.

RESULTS

Comparison of general data

The two groups of patients were similar in gender, age, cause of disease, etiology and body mass index (BMI) (all P>0.05, Table 2).

Comparison of the number of patients who were out of vegetative state after treatment

Seven cases (23.33%) in the treatment group and one case (3.33%) in the control group was out of vegetative state 9 months post treatment (P<0.05, Figure 1).

Comparison of pre- and post-treatment CRS-R scores

The pre-treatment CRS-R score was not significantly different between two groups of patients (P>0.05). After treatment, CRS-R scores increased in both groupsof patients (9.23±2.78 *vs*. 4.43±1.06, 7.12±2.91 *vs*. 4.51±1.16, both P<0.001), and the increase was more obvious in the treatment group than in the control group (9.23±2.78 *vs*. 7.12±2.91, P<0.01, Table 3).

Comparison of pre- and post-treatment EEGs

The pre-treatment EEG showed no significant difference between two groups of patients(P>0.05).A significant difference was observed in EEG in the treatment group post treatment as compared to that before treatment (P<0.001), as well as between two groups of patients post treatment (P<0.01, Table 4).

Comparison of pre- and post-treatment BAEPs

The two groups of patients showed no significant

Table 2: Comparison of background data between the two groups (%, $\overline{x}$ ± sd)

Item	Treatment group (n=30)	Control group (n=30)	χ^2/t	p value
Gender (n)			0.271	0.602
Male	14	12		
Female	16	18		
Age (years)	41.3±9.4	41.8±9.9	0.201	0.842
Course of disease (month)	8.6±1.6	9.1±2.2	1.007	0.318
Underlying cause			0.730	0.948
Traffic accidents (n)	16	14		
Traumatic injury (n)	6	8		
Falling from high altitude (n)	4	5		
Fall injury (n)	3	2		
Others (n)	1	1		
BMI (kg/m^2)	24.22±3.22	24.34±3.34	0.142	0.888

BMI: body mass index

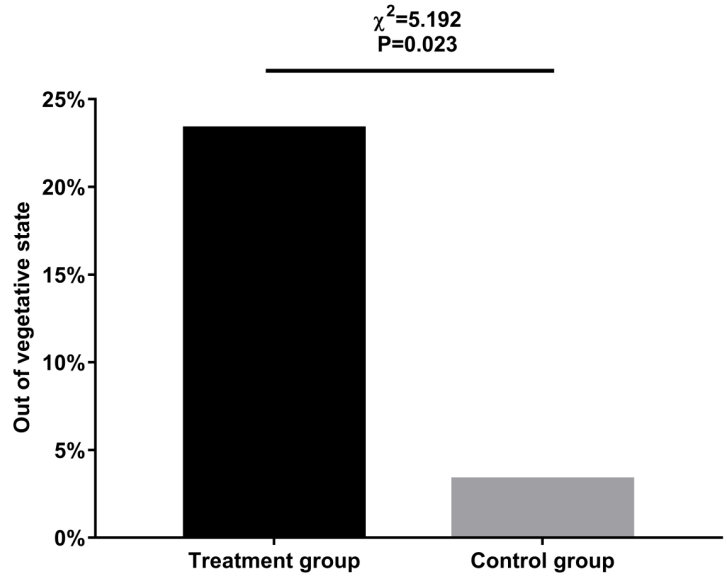

Figure1. Comparison of the number of patients treated without vegetative state between the two groups.

Table 3: Comparison of CRS-R scores before and after treatment between the two groups (scores, $\bar{x} \pm sd$)

Group	Pre-treatment	Post-treatment	t	p value
Treatment group (n=30)	4.43±1.06	9.23±2.78	8.837	<0.001
Control group (n=30)	4.51±1.16	7.12±2.91	4.563	<0.001
t	0.279	2.872		
p value	0.781	0.006		

CRS-R: coma recovery scale-revised

Table 4: Comparison of EEG between the two groups before and after treatment (cases)

Item	Treatment group (n=30)	Control group (n=30)	χ^2	p value
Pre-treatment			0.313	0.958
I	0	0		
II	0	0		
III	3	3		
IV	4	5		
V	8	9		
VI	15	13		
Post-treatment			19.450	0.002
I	3	0		
II	6	1		
III	13	4		
IV	3	8		
V	4	10		
VI	1	7		
χ^2	28.978	4.030		
p value	<0.001	0.402		

EEG: electroencephalogram

difference in the pre-treatment BAEP (P>0.05). But a significant difference was seen in BAEP in the treatment group post treatment as compared to that before treatment (P<0.001), as well as between two groups of patients post treatment (P<0.01, Table 5).

Comparison of pre- and post-treatment SEPs

No significant difference was observed in the pre-treatment SEP between two groups of patients (P>0.05); the post-treatment SEP in the treatment group was significantly different from the pre-treatment level (P<0.01), as well as from that in the control group (P<0.01, Table 6).

Comparison of pre- and post-treatment CBFs

The CBF were similar in two groups of patients before treatment (P>0.05). After treatment, the CBF elevated in both groups (56.32±5.88 *vs*. 44.22±5.21, 51.12±5.56 *vs*. 44.99±5.32, P<0.01), with a greater increase in the treatment group than in the control (56.32±5.88 *vs*. 51.12±5.56, P<0.001, Table 7).

DISCUSSION

In the current study, 7 patients in the treatment group were out of vegetative state after 6 months of treatment, while 1 patient in the control group was out of vegetative state (P < 0.05). CRS-R scores in both groups increased after treatment (all P<0.001), and the degree of improvement in the treatment group was higher than that in the control group (P < 0.01). EEG, BAEP and SEP in the treatment group were better after treatment (all P<0.01), and the improvement in the treatment group was greater than that in the control group (P < 0.01). The cerebral blood flow in both groups increased after treatment (both P<0.001), and the degree of increase in the treatment group was higher than that in the control group (P<0.001).

In this study, 60 patients with PVS were treated with different treatment regimens. It was shown that compared with routine treatment, more patients were out of vegetative state after cSCS treatment, with substantially increased consciousness scores, suggesting that cSCS had a significant effect on PVS patients. Previously, a study enrolled 214 PVS patients who underwent cSCS surgery, had shown that 54% of them improved their consciousness post treatment.[11] Besides, a study from China consisting of 22 patients with severe impaired consciousness. among them 15 were treated with cSCS and 7 were not.[12] The study showed that 9 out of the 15 patients were awake while all 7 patients who did not receive cSCS were not, which confirmed the role of cSCS in the application of PVS patients. Other studies with small sample also showed that cSCS treatment could improve the consciousness of PVS patients and those with minimal disturbance of consciousness, which was in keeping with the results of this study.[19,20] We hypothesized that high cervical spinal cord electrical stimulation could increase CBF and activate cholinergic ascending reticular activating system, which not only improves brain circulation, but also stimulates cerebral cortex, resulting in the patients waking up.

The exploration on the mechanism of cSCS in treating PVS showed that EEG, BAEP

Table 5: Comparison of brainstem auditory induction (BAEP) before and after treatment between the two groups (cases)

Item	Treatment group (n=30)	Control group (n=30)	χ^2	p value
Pre-treatment			0.273	0.872
I	0	0		
II	7	8		
III	9	10		
IV	14	12		
Post-treatment			15.059	0.002
I	8	1		
II	16	9		
III	4	15		
IV	2	5		
χ^2	22.445	4.951		
p value	<0.001	0.176		

BAEP: brainstem auditory evoked potential

Table 6: Comparison of somatosensory evoked potential (SEP) between the two groups before and after treatment (cases)

Item	Treatment group (n=30)	Control group (n=30)	χ^2	P value
Pre-treatment			0.104	0.949
I	0	0		
II	8	7		
III	9	9		
IV	13	14		
Post-treatment			15.059	0.002
I	7	2		
II	15	8		
III	5	12		
IV	3	8		
χ^2	16.523	4.132		
p value	0.001	0.248		

and SEP, which were the three modes of neuroelectrophysiological activities monitored in this study had improved. The neural electrophysiological activity is closely related to the state of consciousness; the anode of electrical stimulation can promote the discharge of adjacent neurons to increase and cause nerve excitement, while the cathode can reduce the release of neuron electricity and reduce the excitability.[21] Clinical studies have shown that electrical stimulation can regulate nerves to achieve the purpose of treating diseases.[22,23] Another clinical trial on the treatment of PVS patients with cSCS also shown that EEG, BEAP and SEP improved in patients with improved consciousness after treatment, and that V wave in BEAP and N20 of SEP were only found in patients with improved consciousness.[24]

This study also measured the CBF of patients before and after treatment, and determined substantially increased CBF of PVS patients after cSCS treatment, suggesting that cSCS can change the cerebral blood supply of PVS patients, which is also an important reason for the wakening and consciousness improvement of patients. Previous evidence has pointed out that the CBF can increase by 40-170% after cSCS treatment for cerebral ischemia patients, effectively improving the blood supply and oxygen supply to the brain and promoting disease recovery.[25] Another research showed a 130% increase in CBF and a significant improvement in limb movement in an ischemic stroke patient one week after cSCS treatment.[26]

In addition, cSCS treatment has been shown to be able to activate the brainstem reticular structure-thalamus-cortex pathway to regain consciousness.[27] Also, cSCS can increase hormone levels in cerebrospinal fluid of PVS patients, such as dopamine and norepinephrine, which is beneficial to the recovery of patients' consciousness.[28]

The mechanism of action of cSCS remains poorly elucidated, but it mainly involves the following: (1) Increasing the whole CBF. In a rat model of subarachnoid hemorrhage, electrical stimulation of bilateral cervical spinal cord reversed the contraction of basilar artery and increased the whole CBF. (2) Activating the brainstem reticular structure-thalamus-cortex pathway to enhance the projection to the cerebral cortex, so as to facilitate the regain of consciousness. (3) Affecting the changes of neurotransmitters in the relevant awakening areas of the brain. cSCS can increase the levels

Table 7: Comparison of cerebral blood flow between the two groups before and after treatment (Vm, $\bar{x} \pm sd$)

Item	Pre-treatment	Post-treatment	t	p value
Treatment group (n=30)	44.22±5.21	56.32±5.88	8.436	<0.001
Control group (n=30)	44.99±5.32	51.12±5.56	4.363	<0.001
t	0.566	3.521		
p value	0.573	<0.001		

of dopamine and norepinephrine in cerebrospinal fluid of patients with coma and PVS. But whether cSCS acts through biochemical, mechanical or other factors and how it increases CBF remains to be explored. Based on this study, we think that both the neurophysiological activities and the change of cerebral blood flow may be the clinical indicators that affect arousal. The average cost of 30 patients treated with cSCS intervention was about 150,000 yuan, which is still within the range that Chinese families can afford.

The limitations of this study were first, the sample size was small and can be further expanded in future studies. Second, the follow-up time was short, which can be prolonged in future studies. Third, the mechanism of cSCS in the treatment of PVS can be further explored.

In conclusion, treatment of patients with PVS by cSCS can promote the regain of consciousness, enhance neuroelectrophysiological activities and improve CBF, which has certain clinical research value, but more clinical studies are needed to further confirm its efficacy.

DISCLOSURE

Conflict of interest: None.

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