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Research Progress of Vagus Nerve Stimulation in Stroke Rehabilitation Treatment

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Abstract: *Background:* Stroke is the leading cause of adult death in China and the leading cause of death worldwide, characterized by high morbidity, disability, mortality, recurrence and economic burden, often leading to various functional impairments, such as motor impairment, sensory impairment, swallowing impairment, consciousness impairment and cognitive impairment. Therefore, finding effective intervention methods is currently a hot and difficult issue in stroke rehabilitation treatment. Vagus nerve stimulation, as a classical neuromodulation technique, has been widely certified for its safety and effectiveness. In recent years, several studies at home and abroad have reported that VNS can be used as a potential rehabilitation treatment to improve functional impairment after stroke. *Objective:* In this paper, the clinical application of vagus nerve stimulation in different dysfunctions after stroke is discussed in the context of relevant studies at home and abroad, and the effectiveness, safety and possible mechanisms of action of VNS in stroke treatment are reviewed, aiming to provide new therapeutic ideas for stroke rehabilitation. *Conclusion:* Vagus nerve stimulation, a classical neuromodulation technique, can help improve various dysfunctions after stroke and improve patients' survivability and quality of life. Vagus nerve stimulation is expected to be a potential new therapy for stroke rehabilitation and play an important role in the rehabilitation of post-stroke dysfunction.

Keywords: Stroke, Vagus Nerve Stimulation, Rehabilitation

1. Introduction

Stroke is a common clinical acute cerebrovascular disease and the leading cause of death and disability among adults in China. [1] The China Stroke Report 2020 shows that the standardized prevalence of stroke in the population aged 40 years and older in China increased from 1.89% in 2012 to 2.58% in 2019, and the number of people aged 40 years and older who have and have had stroke in China is about 17.04 million by 2019, making China the country with the highest risk of stroke and the highest disease burden. [2] More than 70% of stroke patients are unable to live independently due to functional impairment, often leaving physical dysfunction including motor dysfunction, sensory impairment, speech impairment, swallowing difficulties, consciousness impairment, cognitive dysfunction, and depression and anxiety. [3] Conventional stroke rehabilitation mainly consists of physical therapy, occupational therapy, and speech therapy. However, with these conventional approaches, many stroke survivors still have residual functional impairments of varying degrees that impair their ability to perform activities of daily living. [4] In recent decades, rehabilitation techniques have advanced, but how to restore functional impairment in stroke patients remains a key focus and difficulty in the field of rehabilitation.

Vagus nerve stimulation is a neuromodulation technique that sends pulses to the center by stimulating the vagus nerve to treat the corresponding disorder. It was approved by the Food and Administration (FDA) in 1997 for the treatment of epilepsy, depression and headache, and is now an important research topic in stroke rehabilitation. [5] It mainly includes implantable Vague Nerve Stimulation (VNS) and Transcutaneous Auricular Vagus Nerve Stimulation (taVNS). [6] In recent years, vagus nerve stimulation has been reported both nationally and internationally as an effective treatment for stroke patients, with a protective effect against ischemic stroke. [7, 8] In this paper, we review the clinical applications, possible mechanisms and safety of vagus nerve stimulation for different functional impairments after stroke, with the aim of providing new ideas for stroke rehabilitation treatment.

2. Clinical Application of Vagus Nerve Stimulation in Stroke

2.1. Vagus Nerve Stimulation in Post-Stroke Dyskinesia

About 90% of stroke patients are often left with motor dysfunction, which not only severely affects patients' independent walking and living ability, but also has a significant impact on their overall recovery and functional independence. [9, 10] In recent years, several clinical studies have suggested that vagus nerve stimulation has gradually shown a positive effect on the treatment of post-stroke motor deficits, helping to improve motor function after stroke.

Dawson et al [11] randomized 21 patients with moderate to severe upper extremity motor deficits more than 6 months after stroke into a rehabilitation group alone and a VNS+rehabilitation group. Patients who received vagus nerve stimulation showed greater improvement in Fugl-Meyer Assessment Upper Extremity Scale (FMA-UE) scores than those who received rehabilitation alone. Subsequently, Dawson et al [12] again randomized 108 patients with moderate to severe upper extremity motor deficits more than 9 months after stroke into 2 groups, with the treatment group being the VNS+rehabilitation group receiving 0.8 mA, 100 μs, 30 Hz stimulation pulses for 0.5 seconds and the control group being the rehabilitation group alone receiving 0 mA pulses. The treatment was performed 3 times a week for a total of 6 weeks, with a 3-month follow-up after the treatment. The results suggested that approximately twice as many patients in the VNS group achieved clinically meaningful improvement in FMA-UE scores as in the control group, and that the response rate to the Wolf motor function test (WMFT) was higher in the VNS group, and that VNS may also have a "long duration effect". "Kimberley et al [13] randomly divided 17 patients more than 4 months after stroke into 2 groups, the control group received conventional rehabilitation and the treatment group added VNS to this group, and the clinical effectiveness of FMA-UE at day 90 was 88% and 33% in the VNS and control groups, respectively.

Capone et al [14] randomly divided 14 patients more than 1 year after stroke into 2 groups, with taVNS + robotic rehabilitation in the treatment group and robotic rehabilitation alone in the control group. The results showed a significant increase in Fugl-Meyer scores in the taVNS group compared with robotic rehabilitation alone. Redgrave et al [15] randomized 13 patients at least 3 months after stroke into two groups, with the control group having conventional rehabilitation and the treatment group having taVNS added to this group, and the results showed a mean increase in FMA-UE scores in the taVNS group. Wu et al [16] randomized 21 patients with subacute ischemic stroke with unilateral upper limb motor deficits into real or sham taVNS+conventional rehabilitation training groups, and the FMA-UE and WMFT scores improved in both groups, with more significant improvement in the real taVNS group. Li et al [17] randomly divided 60 acute stroke patients into 2 groups to receive taVNS or sham taVNS combined with conventional rehabilitation training. The results showed that after 1 year of follow-up, taVNS combined with conventional rehabilitation training significantly improved motor and sensory function recovery compared to better taVNS combined with conventional rehabilitation training.

2.2. Vagus Nerve Stimulation in Post-Stroke Sensory Disorders

Approximately 11% ~ 74% of stroke patients are often left with sensory dysfunction, commonly with impaired proprioception, stereoacuity and tactile sensation, and associated with a poor prognosis [18]. Recent relevant studies in animals have demonstrated the effectiveness of pairing VNS with sensory retraining. [19] The delivery of short pulses of VNS during tactile rehabilitation resulted in substantial and lasting improvements in sensory function. [20] Also, several clinical studies have preliminarily confirmed that vagus nerve stimulation contributes to the recovery of sensory dysfunction after stroke.

Kilgard et al [21] reported a case of a patient with post-stroke sensory impairment who received implantable VNS combined with sensory training of the upper extremity. The subject was asked to locate, identify and explore various everyday objects while blindfolded, and the results showed significant improvements in tactile thresholds, joint position sense and stereoscopic recognition, suggesting the hypothesis that VNS combined with sensory training may be a new rehabilitation method to promote synaptic plasticity and recovery of sensory function in patients with chronic stroke.

Baig et al [22] recruited 12 patients with moderate to severe upper extremity weakness more than 3 months after stroke who received taVNS for 6 weeks and showed significant improvement in upper extremity sensory function after taVNS treatment.

2.3. Vagus Nerve Stimulation in Post-Stroke Dysphagia

Between 42% and 67% of stroke patients have varying degrees of swallowing disorders. [23] Swallowing disorders can seriously affect the patient's feeding function and lead to poor nutritional status, which not only shortens the survival time and affects the quality of survival, but also seriously affects the prognosis of stroke patients and even leads to death. [24] Vagus nerve stimulation, a novel neuromodulation technique, has been gradually applied to post-stroke swallowing disorders in recent years.

Yuan et al [25] reported a patient with dorsolateral medullary infarction 6 months later with severe dysphagia who received 6 weeks of cervical transcutaneous vagus nerve electrical stimulation, which showed significant improvement in swallowing function and slow pharyngeal peristaltic tract and complete transoral feeding after treatment. Wang et al [26] randomized 40 acute stroke patients into 2 groups to receive taVNS or sham taVNS combined with conventional rehabilitation training for 30 minutes five times a week for 3 weeks. The results showed that the modified Mann Swallowing Ability Assessment Scale, Functional Communication Test of Swallowing score, Rosenbek Leakage-False Aspiration Rating Scale score and clinical changes were greater in the taVNS group compared with the control group, and this improvement persisted for at least 4 weeks after the end of treatment.

Lin et al [27] randomly divided 28 patients with post-stroke dysphagia into 2 groups, with the treatment group receiving magnetic stimulation at 5 Hz at the left mastoid and the control group receiving sham stimulation for 2 weeks. The results suggested that compared with the control group, the vagus nerve stimulation group showed significant improvement in the wave amplitude and latency of the misaspiration scale and the Australian Treatment Outcome-Swallowing Scale, radiography, and cricopharyngeal muscle motor evoked potentials, and vagus nerve magnetic stimulation could effectively restore swallowing function after stroke.

2.4. Vagus Nerve Stimulation in Post-Stroke Disorders of Consciousness

Clinically, post-stroke impairment of consciousness often manifests as drowsiness, somnolence, coma, agitation, and delirium. [28] It has been shown that about 4% ~ 38% of stroke patients have varying degrees of coma, and 13% ~ 48% of stroke patients have delirium and delirium. [29] Impaired consciousness after stroke prolongs the recovery time of patients, affects their function and prognosis, and places a heavy psychological and physical burden on their families and society. [30] Recent studies have shown that vagus nerve stimulation can improve the level of arousal in comatose patients with craniocerebral injury. [31]

Yifei et al [32] recruited 12 patients with impaired consciousness (8 with stroke; 2 with hypoxia; and 2 with traumatic brain injury) and randomized them to taVNS or transcutaneous non-auricular VNS (tnVNS) groups. taVNS group received bilateral auricular region stimulation parameters of 4-6 mA at 20 Hz for 30 min each, 2 times/day for 14 days. The tnVNS group applied VNS to the bilateral auricular anlage zone (the caudal part of the helix, which is considered to be devoid of vagal innervation). The results showed that resting-state EEG power spectra of patients in the taVNS group with a minimally conscious state showed a decrease in δ-band energy and an increase in β-band energy with better consciousness, whereas there was no significant change in the tnVNS group. taVNS may be a possible treatment for consciousness disorders. Wang et al [33] collected data from 17 patients with chronic disorders of consciousness who received VNMM and showed that all patients showed behavioral improvements after 4 weeks of VNMM intervention, with significant improvements in the Revised Coma Recovery Scale, Glasgow Coma Score, indicating that VNMM can promote recovery of the conscious state in patients with chronic disorders of consciousness.

2.5. Vagus Nerve Stimulation in Post-Stroke Cognitive Impairment

Post-stroke cognitive impairment is a common sequela of stroke, present in 17.6% ~ 83% of stroke patients, and often manifests as varying degrees of impairment in memory, attention, executive function, language and visuospatial function, which not only leads to disability, high dependency and low quality of life in stroke patients, but is also strongly associated with high recurrence rates and low survival. [35, 36] Recently, vagus nerve stimulation has been suggested to have the potential to improve cognitive impairment. [37-39]

Thakkar et al [40] reported that taVNS at 5 Hz and 200 μs increased automaticity and decoding task performance, improved reading ability, and had potential effects on a wide range of cognitive functions. Some clinical trials have shown that vagus nerve stimulation can promote recovery of learning and memory functions in stroke patients. [41]

At present, vagus nerve stimulation for post-stroke cognitive impairment rehabilitation is still at the initiation stage, and there are relatively few relevant clinical studies conducted, which are not systematic or in-depth enough and need to be further explored.

3. Possible Mechanisms of Vagus Nerve Stimulation for Stroke

3.1. Anatomical Access

The vagus nerve consists of a mixture of 80% afferent sensory fibers and 20% efferent fibers. [42] The majority of the afferent branches of the vagus nerve project to the bilateral solitary nucleus of the medulla oblongata and subsequently project from the solitary nucleus to the basal nucleus, the nucleus accumbens, the thalamus, the limbic system, and the cerebral cortex. [43] Throughout the conduction pathway, the stimulus is afferent from the vagus nerve to the nucleus tractus solitarius and then releases norepinephrine levels in the cerebral cortex via the control of the nucleus accumbens. [44]

3.2. Anti-Inflammatory Effect

The anti-inflammatory effects of the vagus nerve are neuroprotective through the classical cholinergic anti-inflammatory pathway that activates the release of acetylcholine from α7 nicotinic acetylcholine receptors on microglia, which in turn inhibits the inflammatory response induced by stroke. [7] It also downregulates pro-inflammatory genes, reduces the release of pro-inflammatory factors (as interleukin 1β, tumor necrosis factor-α) in the peripheral circulation, and alleviates tissue damage, thereby promoting functional recovery after stroke. [45]

3.3. Blood-Brain Barrier Protection

The integrity of the blood-brain barrier plays an important role in intracerebral homeostasis, which is often disrupted and forms edema in stroke patients. Vagus nerve stimulation can protect the blood-brain barrier, reduce the extent of cerebral ischemic infarction, and alleviate neurological deficits in injured brain regions. [46] However, the specific mechanism of vagus nerve on blood-brain barrier repair still needs to be further investigated.

3.4. Increase the Plasticity of Nerves

Enhanced neuroplasticity by vagus nerve stimulation is the main mechanism of functional recovery after stroke. Stimulation of the vagus nerve releases neurotransmitters, such as norepinephrine and acetylcholine, throughout the cerebral cortex by activating the nucleus basalis and nucleus accumbens, while vagus nerve stimulation increases the levels of brain-derived neurotrophic factor and basic fibroblast growth factor, and vagus-neurotrophin together enhances neuroplasticity and promotes neural regeneration and brain network remodeling. [47]

3.5. Other

In addition to these possible mechanisms, other studies have shown that vagus nerve stimulation may also be associated with anti-apoptotic effects, [48] antioxidant effects, [49] and regulation of blood perfusion. [50]

4. Safety and Adverse Effects of Vagus Nerve Stimulation

Most of the adverse effects of implantable VNS are procedure-related, and common side effects are hoarseness, sore throat, cough, shortness of breath, surgical site infection, tingling, and muscle pain, etc. In general, most stimulation-induced symptoms can be minimized by reducing the intensity of stimulation and most patients recover, but still at least two patients experienced permanent vocal cord paralysis a few weeks after implantation, which may be related to the traction exerted on the recurrent laryngeal nerve by the patients themselves when operating the device. [51]

Transcutaneous VNS is a noninvasive neuromodulation technique that allows non-invasive stimulation of the vagus nerve and is safer and better tolerated compared to implantable VNS. Redgrave et al [52] analyzed 51 studies totaling 1322 subjects who received transcutaneous VNS from 1996 to May 2017. The most common side effects were local skin irritation due to electrode placement, headache and nasopharyngitis. A total of 30 serious adverse reactions occurred, but only three were assessed by the researchers involved as possibly caused by percutaneous VNS.

5. Conclusion

In conclusion, vagus nerve stimulation, as a classical neuromodulation technique, can help improve functional impairment after stroke and enhance patients' survival and quality of life. Traditional implantable VNS has limited clinical application due to its inherent drawbacks, while non-invasive VNS has more potential for future development. Currently, most of the research related to vagus nerve stimulation is focused on motor dysfunction, and there is still a broad development prospect and application market in the field of stroke rehabilitation. However, there are still some problems in the current research on this technique: (1) the mechanism of action of VNS is not yet completely clear, and the mechanisms of action and their interactions need to be further explored; (2) the sample size of studies on VNS as a post-stroke rehabilitation intervention is generally small, and more randomized, double-blind, and reasonable sample sizes are needed; (3) there is a lack of uniformity in VNS stimulation parameters, stimulation duration, and other factors. In future studies, it is recommended to combine VNS with neuroimaging techniques to study the pathophysiological mechanisms of disease development in order to find out the optimal stimulation parameters and stimulation duration.

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