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Effect of Vagus Nerve Stimulation on Ischemic Stroke: Review Article

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Abstract:

Purpose of Review: Vagus nerve stimulation (VNS) has introduced as a potential therapeutic modality for many neurological diseases. In recent years, there is an increasing interest in VNS for treating ischemic stroke. This review aimed to illustrate and discusses the evidence supporting VNS as a treatment option for ischemic stroke.

Methods: We searched Science Direct, Google Scholar, and PubMed for, ischemic Stroke, non- invasive vagus nerve stimulation, stroke recovery and cognitive function in stroke. The authors also reviewed references from pertinent literature, however only the most recent or comprehensive studies from December 2011 to February 2024 were reviewed. Documents in languages other than English were disqualified due to lack of translation-related sources. Papers such as unpublished manuscripts, oral presentations, conference abstracts, and dissertations that were not part of larger scientific studies were excluded.

Results: VNS combined with traditional rehabilitation approaches can improve functional and cognitive outcomes in ischemic stroke. Further high quality studies are necessary to support the evidence-based practice of this stimulation approach.

Conclusion: A review of the current literature concluded that using VNS can enhance motor, sensory and cognitive recovery in ischemic stroke.

Keywords: Ischemic stroke, non- invasive vagus nerve stimulation, stroke recovery, cognitive function.

Introduction

Stroke is the second leading-cause of death and disability worldwide. It causes 11.6% of total deaths worldwide. The annual number of strokes and deaths due to stroke increases every year. From 1990, incidence of stroke increased by 85 %, deaths from stroke increased by 43 %, and disability due to stroke increased by 32% worldwide [1]. Stroke is a neurological deficit attributed to an acute focal injury of the central nervous system (CNS) due to vascular causes. Vascular causes of stroke are cerebral infarction, intracerebal hemorrhage (ICH) and subarachnoid hemorrhage (SAH). Ischemic stroke is the most common types of stroke. It represents 62.4% of all incident stroke cases worldwide (7.63 million). Ischemic stroke is defined as an episode of neurological dysfunction caused by focal cerebral infarction. Cerebral infarction is defined as the death of brain cells due to focal ischemic injury in the cerebral vessels. Ischemia may be due to vascular occlusion, causing loss of electrical function and progresses to disturbance of membrane function, generation of reactive oxygen species, destruction of cell membranes and death of cells [2].

Stroke causes several neurological deficits or impairments as hemiparesis, communication disorders, cognitive deficits or disorders in visuo-spatial perception. Approximately 60% of survivors after stroke suffer from upper and lower limb motor impairment, which lead to loss of independence with poor quality of life [3, 4]. These global economic and social costs of chronic disability due to stroke necessitate the development of new methods beside the conventional treatment to enhance stroke recovery [5]. Vagus nerve stimulation (VNS) is a neuromodulatory therapy, which sends impulses via the vagus nerve into the neural center to generate corresponding nervous activity [6, 7]. Vagus nerve stimulation is an established treatment in epilepsy, depression, chronic tinnitus, migraine and chronic pain [8-12]. Vagus nerve stimulation also shows a positive effect for the treatment of motor impairment after the stroke [13].

Types of vagus nerve stimulation:

Vagus nerve stimulation (VNS) is a medical procedure that involves delivering electrical impulses to the vagus nerve. There are two clinical methods for vagus nerve stimulation: invasive VNS and noninvasive VNS. Invasive VNS (iVNS) is clinically performed by implanting of a pacemaker-like device that works by stimulating electrodes connected to the left cervical vagus nerve with wires connected to via an implanted pulse generator (IPG) surgically implanted in the chest[14]. Invasive Vagus nerve stimulation (iVNS) is an approved treatment for epilepsy, as well as a therapeutic option for many disorders such as depression, anxiety, and Alzheimer’s disease. In ischemic stroke, iVNS paired with intensive motor training can improve motor function [8, 10, 14]. Unfortunately, the iVNS has many disadvantages such as high cost, irreversibility of the electrode implant and many side effects related to surgical implantation (e.g. infection, dysphagia, shortness of breath; hoarseness of voice and vocal cord paralysis [15].

Noninvasive VNS is achieved through transcutaneous vagus nerve stimulation by the conventional transcutaneous electrical nerve stimulation (TENS). Transcutaneous VNS (tVNS) is an effective, inexpensive, well-tolerated and safe method for modulating the vagus nerve [16].Transcutaneous vagus nerve stimulation (tVNS) can be applied on the cervical branch of the vagus nerve supplying the neck, called transcutaneous cervical vagus nerve stimulation (tcVNS) or on the auricular branch of vagus nerve supplying the ear, called transcutaneous auricular vagus nerve stimulation (taVNS) [17]. Both taVNS and tcVNS are used for tVNS in clinical trials but the taVNS is the

commonest used methods due to safety considerations. The cervical vagus nerve supply the heart, with the right cervical vagus predominantly innervates the sinus-atrial node (SAN), whereas the left-cervical vagus nerve predominantly innervates the atrial–ventricular node (AVN). The right tcVNS can cause significant cardiac side effects as bradycardia, whereas the left tcVNS causes no such effects. As a result, left tcVNS provides more safety than the right tcVNS [18].
The auricular branch of the vagus nerve is the only afferent branch of the vagus nerve distributed on the surface of the skin. It supplies the medial side of tragus, the external auditory canal, the medial side of antitragus, the cymba concha and the cavum concha [6, 19]. However, the two most common sites for taVNS are tragus and the cymba conchae [20]. A functional magnetic resonance imaging (fMRI) study showed that the cymba concha is the most effective and optimal location for taVNS therapy [21].The taVNS can be applied on either the right or left auricular vagus nerve but most clinical trials applied taVNS on left auricular vagus to avoid any undesirable effects on heart. However, it is found that afferent input from both sides is centrally integrated in nucleus of solitary tract (NST), resulting in the same physiological effects by sending signals through the efferent of bilateral cervical vagal nerves to the heart [18].

Application of vagus nerve stimulation in clinical studies of ischemic stroke:

Application of iVNS in ischemic stroke:
The iVNS showed a highly positive effect on motor, sensory and cognitive function in both animal and human studies of ischemic stroke. In rats, invasive VNS combined with rehabilitation can enhance cortical plasticity and forelimb strength in rats with cerebral infarction. It can also treat elderly rats with ischemic stroke [22, 23]. Furthermore, iVNS can significantly improves spatial and fear memory in rats with ischemic stroke [24]. In human studies, iVNS combined with rehabilitation can improve the motor functional scores in chronic stroke patients [14].

Application of non-invasive VNS in ischemic stroke:
Non-invasive VNS has a similar effect as invasive VNS in both animal and human studies. The tcVNS could reduce myocardial infarct size and improve cerebral function in rats. In addition, improvements in forelimb motor function were sustained even after termination of tcVNS stimulation [25]. While, taVNS paired with motor training can increase upper limb motor and sensory function in chronic ischemic stroke patients [16, 26, 27]. Also, taVNS paired with tactile training can improve tactile thresholds, proprioception, and stereognosis in patients with chronic stroke [28]. Furthermore, addition of taVNS before upper limb rehabilitation is associated with significant improvements in motor function of stroke patients [29]. The effect of non- invasive VNS on cognitive function in stroke patients is still not widely explored in human studies. However, a single previous study showed that a single session of tVNS cannot improve cognitive functions in post-stroke patients.

Possible mechanisms of VNS in acute and chronic ischemic stroke:
The underlying mechanism of VNS action is different in acute and chronic stages of stroke. In acute stroke, VNS can reduce the lesion size, suggesting that brain protection, neural regeneration, angiogenesis, and neuroplasticity are the fundamental mechanisms of VNS activity. The vagus nerve connects the immune and central nervous systems. So, it plays a significant role in regulating neuroinflammation that begins few hours after ischemic stroke [31-34].

In chronic stroke, inducing neural plasticity is the most likely mechanism of VNS in chronic stroke rather than neural protection. Experimental studies support this idea showing that VNS can improve levels of brain-derived neurotrophic factor (BDNF) and noradrenaline, which both can boost neural plasticity and recovery after cerebral lesion [35].

Conclusion

It was concluded that adding VNS can improve motor, sensory and cognitive recovery in ischemic stroke.

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Disclosure statement

No author has any financial interest or received any financial benefit from this research.

Conflict of interest

Authors state no conflict of interest.

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