Indonesian Journal of Neurosurgery

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Stimulation of vagal nerve in intracranial hypertension: A literature review

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Received: 2020-12-22

Accepted: 2021-07-29

Published: 2021-08-13

ABSTRACT

Background: Pathologies that affect the central nervous system (CNS) and increases intracranial pressure may develop into fatal outcomes. There are physiological properties of neurons that are susceptible to modify, such as neuronal plasticity. The vagus nerve stimulation (VNS) has focused on the modification of these variables in order to restore the homeostasis of the CNS. In this article, we aimed to review the general concept of VNS, the pathology of intracranial hypertension and the effects of combining treatment to the pathology.

Literature review: VNS activates several neuromodulatory pathways and centers in the brain, which associated with plasticity. They are including cholinergic and noreadrenergic system, which are transcendental for neural plasticity. One of the mechanisms by which VNS decreases ICP is due to the attenuation of the systemic inflammatory response and the signaling of proinflammatory cells induced by TBI, whose possible mechanism is the inhibition of cytokines such as tumor necrosis factor (TNF), IL-1b, IL-6 and IL-18. In addition, it had been shown that VNS stimulated the locus coeruleus with a consequent release of norepinephrine, which act as an endogenous anti-inflammatory agent. VNS requires neuroanatomical knowledge of the entire vagal network and its physiology. The surgery is relatively simple and the complication rates are very low conferring a great effectiveness in several neural diseases. Neural and non-neural pathways have been well-characterized to avoid the immune response through VNS.

Conclusion: Different experimental studies have concluded that VNS reduces intracranial pressure, although the mechanism is not completely specified. Further studies evaluating the clinical role of VNS in intracranial hypertension are necessary.

Keywords: intracranial hypertension, vagus nerve, vagus nerve stimulation

Cite This Article: García-Ballesteras, E., Durango-Espinosa, Y., Mendoza-Flórez, R., Agrawal, A., Deora, H., Matallana-Ramírez, L., Joaquim, A.F., Moscote-Salazar, L., . 2021. Stimulation of vagal nerve in intracranial hypertension: A literature review. *Indonesian Journal of Neurosurgery* 4(2): 21-26. DOI: 10.15562/ijn.v4i1.109

INTRODUCTION

Pathology in the brain leads to abnormal function of the nervous system.¹ The mass effect created by certain pathologies can result in a syndrome of systemic inflammatory response, sepsis and multi organ failure.^{2,3} Recently, the therapy that aiming to modify plasticity (neuromodulation) had been explored.¹ Neuromodulation is a therapy consisting by administering energy to the nervous system to excite, inhibit or modify neural activity to modify the natural course of a certain disease.³

At the end of the nineteenth century, it was known that the parasympathetic nervous system was compromised in certain diseases. In 1884, Corning performed first transcutaneous electrical

stimulation of the vagus nerve to modify certain cardiovascular parameter.⁴ Unfortunately, it did not succeed, but it was the beginning of a new era to treat pathologies of the nervous system.⁵ Since then, several findings had strengthened the theoretical basis of technical effects of this practice, which was used to investigate its effects on animals.^{6,7} In humans, it was approved in 1997 to treat epilepsy. Further, it is also approved to treat major depressive disorder and Alzheimer's disease in 2005.^{3,5-7} In present time, it is performed to relieve headaches, arthritis, asthma, joint pain, fibromyalgia, irritable bowel syndrome, gastric motility disorders, obesity, hemostasis, bipolar disorder and dementia.⁵ It had been accepted that vagus nerve stimulation (VNS) provided beneficial effect in the treatment of

intracranial hypertension using brief burst stimuli of vagus nerve¹ or by implanting a subcutaneous pulse generator.³

The VNS was used by more than 50,000 people in the world. It had been postulated that VNS acted through several mechanisms such as reduction of TNF- α ,^{2,6} and proinflammatory interleukins^{3,6}; increase noreadrenaline^{6,8}; and etc., which still the subject of various questions and continuous research.⁶ In this article, we aimed to review the general concept of VNS, the pathology of intracranial hypertension and the effects of combining treatment to the pathology.

INTRACRANIAL HYPERTENSION

The skull cavity contains 70% of neural tissue, 15% of blood and 15%

of cerebrospinal fluid (CSF), which are surrounded by dura mater and bone. The sum of the pressures exerted by each of these components is known as intracranial pressure (ICP), which varies according to age, body position and clinical condition.^{9,10} Brain tissue, CSF and intracranial blood have a combined volume of approximately 1,200 to 1,500 ml and normal ICP is usually between 5 to 15 mmHg in normal condition.^{10,11} Intracranial hypertension is defined as the elevation of the ICP above 20 mmHg, which sustained for at least 10 minutes.^{11,12} The pathophysiology of intracranial hypertension is determined by the Monroe-Kellie doctrine, which states that the total volume of intracranial contents is constant and that any increase in any of those components will initially fill a small potential space of only a few milliliters in volume. Then, it must be compensated by a decrease in the volume of another intracranial component to avoid an increase in the ICP.^{9,10,12} The CSF and intracranial venous blood move to the spinal compartment when the ICP increases due to its capability to diminishes quick and efficient. However, this compensation is limited and ICP may increase rapidly when decompensation occurs.^{9,11} There is a relationship between volume and intracranial pressure. Initially, the pressure increases slightly with the increase in volume, but when the compensation mechanisms are exceeded, the pressure increases rapidly.¹¹

CSF is produced by choroid plexus and circulates through the ventricular system. It is subsequently absorbed by the arachnoid villi and venous granulations.

Any factor that alters the flow of CSF or its absorption in the vasculature can often lead to an increase of the ICP.⁹ Intracranial hypertension decreases cerebral perfusion pressure (CPP), which defined as mean arterial blood pressure (MAP) minus ICP. CPP is the driving force behind cerebral blood flow, and as it decreases, cerebral blood flow can be insufficient for adequate cerebral oxygenation. This process could induce additional cytotoxic edema and result in an even higher ICP.¹¹

Human body has autoregulation mechanisms to maintain blood pressure between 50 and 150 mmHg, either by vasodilatation or vasoconstriction. This autoregulation mechanism maintains adequate cerebral blood flow and reduce injury to the brain parenchyma.^{9,12} In addition, it is important to note that cranial vault is divided into several compartment by dural folds. Because of this, the ICP is not similar throughout the skull cavity. Increases in the contents of a region of the brain can cause regional increases in the ICP. In extreme cases, the contents of that compartment can move, or herniated, to a different compartment.^{9,11,12}

Any condition that alters the intracranial content could cause elevations of the ICP. It is important to understand that the impact of the increase in ICP depends on the cause and the progressivity. Pressure greater than 15 mmHg is poorly tolerated in rapid progression, as in the case of traumatic brain injury (TBI). On the other hand, increased ICP due to tumor gives better adaptation because of slow progression.¹² In **Table 1**, we can see the main causes of intracranial hypertension.

In specific situations such as TBI, disruption of the blood-brain barrier (BBB) leads to accumulation of fluid and active molecules inside the brain parenchyma.¹³ This process leads to cell destruction and produces primary lesions which can lead to post-traumatic pathophysiological consequences, such as cell excitotoxicity, inflammation and cerebral edema that leads to intracranial hypertension.^{3,13}

VAGAL NERVE STIMULATION

Vagus nerve stimulation emerges as a therapy to enhance rehabilitation of various sensory, motor and cognitive neuropathologies by inducing neuroplasticity.¹⁴ Vagus nerve was known providing neuroplasticity due to modulation of central nervous system (CNS) and direct pathway to memory function.¹

The vagus nerve was originated from the brainstem to innervates different thoracoabdominal viscera and responsible for the parasympathetic function of these organs.^{4,5} It receives several sensory pathway to modulate anatomical and functional connections of this nerve, which explain its effects in the CNS.¹⁵ The nucleus of vagus nerve is consisted of four nuclei, which are nucleus of the solitary tract, dorsal motor nucleus of the vagus nerve, spinal nucleus of the trigeminal nerve, and ambiguous nucleus (**Figure 1**).⁴ The fibers of these nuclei converge in a single trunk and emerge from the spinal bulb to traverse the foramen jugulare. Furthermore, it is divided into several terminations (atrial,

Table 1. Main causes of intracranial hypertension¹³

Increase in brain volume	Increase in CSF	Increase in blood volume	Mixed
Space occupying lesion injury:	1. Hydrocephalus	1. Hyperemia	1. Arteriovenous malformations
• Abscess	2. Arachnoid cyst	2. Hypercapnia	2. Hypertensive encephalopathy
• Hemorrhagic contusion	3. Choroidal plexus papilloma	3. Obstruction of blood flow	3. Traumatic brain injury
• Epidural hematoma			4. Subarachnoid hemorrhage
• Subdural hematoma			5. Abdominal hypertension
• Intracerebral hemorrhage			6. Meningitis, encephalitis
• Tumor			
Brain edema:			
• Metabolic encephalopathy			
• Anoxia			

meningeal, sympathetic, pharyngeal and cardiac), some of which are subdivided into nervous plexus (cardiac, pulmonary, esophageal, celiac, myenteric, adrenal, hepatic and gastroduodenal).^{4,5}

More than 80% of the fibers (all of which are composed of fibers A, B and, mostly C) are directed to nucleus of solitary tract. In nucleus of solitary tract, it releases excitatory neurotransmitters such as glutamate and aspartate. They have capability to inhibit γ -aminobutyric acid (GABA), acetylcholine, nitric oxide, vasoactive intestinal peptide and other neuropeptides for signal transduction.⁵ The efferent fibers of nucleus solitary tract to mesencephalic nuclei such as locus coeruleus and dorsal raphe magnus release norepinephrine and serotonin to entire

brain.¹⁵ The afferent fibers are mainly from the postrema area, the spinal nucleus of the trigeminal nerve and the nucleus of solitary tract. The neurons of these fibers form superior and inferior ganglia, which are jugular and nodose, respectively.⁵

This vagal system regulates various sensory functions and provides homeostatic regulation of different cardiovascular variables (blood pressure, heart rate, vascular resistance, respiration, feeding and diameter of the airways), digestive (peristalsis) and neuroendocrine system.⁵ Tyrosine hydroxylase has been isolated from vagal neurons, an enzyme that intervenes in the metabolism of norepinephrine and dopamine. Therefore, it is believed that there is a sympathetic function in these neurons.⁵

Figure 1. Vagus nerve anatomy. Each arrow shows the unidirectional conduction. DMN: dorsal motor nucleus; NA: nucleus ambiguus; SF: sympathetic fibers; NST: nucleus of the solitary tract; SNT: nucleus of the trigeminal nerve.

The right VNS is intended for the treatment of heart failure, so it will not be mentioned in this literature.⁵ The vagus nerve stimulation therapy equipment is composed of a programmable pulse generator, a bipolar helical electrode, a programming stick linked to a software that allows programming and evaluation, a tunneling tool and magnets. Each stimulation period is preceded by 2 seconds of acceleration time, followed by 2 seconds of reduction ramp time.¹⁶

The surgical procedure to put left cervical vagal stimulator requires general anesthesia. Incision on lateral of pectoralis major muscle is performed to put the generator. The second incision is on the neck where the electrode cable is attached to the left mid-cervical vagus nerve and thus the conductor cable passing through a subcutaneous tunnel to be connected to the generator. This is an ambulatory procedure and usually lasts from 1 to 3 hours under general anesthesia.¹⁷

The programmable parameters are the current load (intensity of the electrical stimulus, measured in miliamperes (mA)), which is 0.25 mA initially; the width of the pulse (duration of the electrical pulse, measured in microseconds), 250 – 500 μ s initially; the pulse frequency (measured in Hertz (Hz)), which is 30 Hz initially; and the activation/ deactivation of the working cycle (the stimulus on and off, measured in seconds or minutes).¹⁵ The optimal configuration is still unknown but the most prudent thing to do is start at low frequencies.⁵ By placing the programming stick on the generator, the software allows us to read and alter the stimulation parameters.¹⁶ It also contains mechanical and electrical safety features that reduce the possibility of high frequency stimulation that could cause tissue damage.¹⁷ Therefore, the moderate intensity stimulation produces a cortical motor reorganization greater than the low or high stimulation.¹⁴ The generator works continuously, but each patient is given a magnet to deactivates the stimulation if placed on the pulse generator. The generator should also be deactivated when withdrawing the normal programmed stimulation.^{5,17}

The electrical stimulation of the vagus nerve stimulates activity in the

anterior cholinergic basal brain and the noreadrenergic locus coeruleus, leading to the subsequent release of neuromodulators throughout the cortex. Both of neuromodulator system are essential for cortical neuroplasticity.¹ VNS adjusts norepinephrine levels in the brain and promotes recovery.⁶ It is necessary to emphasize that the activation of the locus coeruleus following VNS directly influences the cerebral cortex. Locus coeruleus innervates almost all levels of the central nervous system because it is the only sources of norepinephrine of the cerebral and cerebellar cortices.⁴

Adverse events are mostly related to the surgical procedure or to the electrical stimulation itself. Adverse events related to the surgical procedure include peritracheal hematoma or vagus nerve trauma. Surgical complications are rare, but it is known that during surgery, bradycardia and asystole may occur during the guide impedance test.⁵ Adverse events related to stimulation include voice disturbance, cough, dyspnea, headache and paresthesia in the left cervical region.^{5,15-17} Long-term arrhythmias and delayed syncopes have been reported.⁵ Vagus nerve stimulation may have an unfavorable impact on sleep breathing disorders (obstructive sleep apnea).¹⁶

SURGICAL TECHNIQUE

The implantation of the right and left vagus nerve stimulator had shown similar efficacy. However, left side was preferred to avoid cardiovascular side effects due to innervation of the right vagus nerve to sinoatrial node.¹⁸ It is necessary to prepare atropine and catecholamines in case of bradycardia and asystole during intraoperative stimulation.¹⁹

Two incisions are made, one in the neck for the implantation of the electrodes and one in the chest for the implantation of the impulse generator. First incision is made in skinfold of the neck at midpoint between the mastoid and the clavicle 3 to 4 cm in length, from the midline to the medial border of the sternocleidomastoid.¹⁸ The second incision should be made a little above the axillary fold, medial to the shoulder joint. The platysma is divided and retracted, the deep cervical fascia is opened in the anterior border of the

sternocleidomastoid muscle and the medial blunt dissection is performed. Identification of ansa cervicalis should be done and should not be confused with vagus nerve, subsequently dissects the loop.¹⁹ At this point, the procedure should continue using the operating microscope or the surgical loops. Dissection of the nerve of the carotid is performed with a blunt hook and then dissect the vagus nerve carefully (to preserve the vasa nervorum intact) with the help of a loop in a length of 3 to 4 cm.¹⁸

First, the anchor is placed comfortably around the nerve allowing minimal movements. After that, we place the positive (central) and negative (upper) electrodes. Next, the electrode impedance is tested together with the generator function. After this, a medial subcutaneous pouch is formed to the armpit or to the breast, 5 cm in length and height. The stimulator cable is placed by passing the tunneling device from the subcutaneous pouch to the cervical incision, where the electrode is anchored at two points to the silicone supports in the deep cervical fascia and near the sternocleidomastoid muscle. The battery is fixed to the lead electrode and anchored by nonabsorbable sutures to the fascia of the pectoral muscle. Finally, the two wounds are closed in anatomical layers using absorbable sutures.^{18,19}

MECHANISM OF ACTION OF VNS

Synaptic plasticity is the most important point of restoration following TBI, which occurs due to synaptogenesis. It is believed that VNS could enhance synaptic plasticity and provided neuroprotective effects (Figure 2).^{6,20} VNS activates several neuromodulatory pathways and centers in the brain, which associated with plasticity. They are including cholinergic and noreadrenergic system, which are transcendental for neural plasticity.²⁰ One of the mechanisms by which VNS decreases ICP is due to the attenuation of the systemic inflammatory response and the signaling of proinflammatory cells induced by TBI, whose possible mechanism is the inhibition of cytokines such as tumor necrosis factor (TNF), IL-1b, IL-6 and IL-18.^{2,3,6,13,15} In addition, it had been shown that VNS stimulated the locus coeruleus with a consequent release of norepinephrine, which act as an endogenous anti-inflammatory agent.^{3,6,7,15,21,22} Norepinephrine also has protective role in vasogenic edema following TBI due to regulation of cerebral blood flow.⁷ Norepinephrine levels also reported increase in amygdala, hippocampus, and cerebral cortex of rats following VNS.²² Furthermore, it

Figure 2. Different pathways of mechanisms of VNS.

had been shown that VNS increased plasma levels of ghrelin, which provided neuroprotection following brain injury indicated by reduction of cerebral edema and inflammatory cytokines.^{2,3,6,13} In addition, it was shown that ghrelin negatively regulated TNF.⁶

Endotoxemia activated immune response, which originated in the spleen. An indirect parasympathetic autonomic regulation (by preganglionic fibers of the celiac ganglia) and direct sympathetic (postganglionic fibers) induced release of TNF- α by the splenic macrophages. VNS does not act through this autonomic pathway, but through a non-neural peripheral pathway called the cholinergic anti-inflammatory pathway, which involves nicotinic cholinergic receptor- $\alpha 7$ ($\alpha 7$ nAChR). VNS stimulates release of acetylcholine from the celiac ganglion on the spleen, resulting in a release of norepinephrine that interacts with $\beta 2$ AR receptor cells containing choline acetyltransferase for the synthesis of acetylcholine. They will be released and act through $\alpha 7$ nAChR in splenic macrophages and downregulate the expression of NF κ B / STAT3, decreasing TNF- α , box 1 of the high mobility group and other cytokines that are expressed before the endotoxemic stimulus.

In the case of TBI, cell excitotoxicity, inflammation, and cerebral edema may cause an increase in ICP.^{3,6} Patients with increased ICP following TBI are associated with a worse prognosis.³ For this reason, an important objective when treating a severe TBI is to find a way to control the ICP and cerebral perfusion in a timely manner. Neuromodulation techniques have been accepted as a treatment for various neurological and psychiatric pathologies. In recent years, VNS have been investigated as a treatment for TBI with very promising results.³

EXPERIMENTAL STUDIES ADDRESSING VNS AND ICP

Clough, *et al.* evaluated the ability of VNS to reduce cerebral edema in traumatic brain injured rats.⁷ They reported a remarkable and statistically significant decrease of edema at 2 days. Decrease of cerebral edema was

determined by calculating the difference of weight between hydrated and dehydrated (in an oven at 100°C) brain. The percentage of water in the ipsilateral hippocampus in control group was 80.71 ± 0.41 , while in VNS was 80.43 ± 0.34 ($p < 0.041$). However, the reduction was not significant in prefrontal cortex, cerebellum and brainstem. The reduction of edema is indirectly related to the decrease of ICP. However, the mechanism was still unclear.³

Smith *et al.* used a percussion model of brain lesions in rats to show that VNS was able to reduce cortical edema induced by TBI and also improves cognitive function.²² Pruitt *et al.* observed that combination of lower level VNS and rehabilitation training was effective for improvement.²⁰ On the other hand, Lopez *et al.* demonstrated that VNS decreases the permeability of blood-brain barrier in patients with TBI. VNS inhibited high regulation of aquaporin 4 (AQP-4) that was induced by TBI, which contributed to the decrease in cerebral edema and ICP.¹³

Tubbs *et al.* experimented in pigs using VNS with stimulation parameters similar to those clinically used for the treatment of epilepsy.²³ They reported that VNS (especially the left vagus nerve) produced an average reduction of 6 mmHg in ICP within 15 to 35 minutes after stimulating the nerve. It did not cause alterations in cardiovascular responses, such as bradycardia or hypotension.²³ VNS may play a role in controlling the ICP. However, it is necessary to conduct further research to determine applicable conclusions in humans regarding VNS for TBI.⁶

CONCLUSION

VNS requires neuroanatomical knowledge of the entire vagal network and its physiology. The surgery is relatively simple and the complication rates are very low conferring a great effectiveness in several neural diseases. Neural and non-neural pathways have been well-characterized to avoid the immune response through VNS. Different experimental studies have concluded that VNS reduces intracranial pressure, although the mechanism is not completely specified. Further studies evaluating the clinical role of VNS in intracranial hypertension are necessary.

CONFLICT OF INTEREST

There is no conflict of interest related to the materials or methods used in this study.

FUNDING

This article received no specific funding from any funding agency in the public, commercial, or not-for-profit sectors.

AUTHOR CONTRIBUTIONS

Authors took part in design of the study, contributed to data collection, participated in writing the manuscript and all agree to accept equal responsibility for accuracy of the contents of this article.

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