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Transcutaneous Auricular Vagus Nerve Stimulation on Post-Herpetic Neuralgia

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TRANSCUTANEOUS AURICULAR VAGUS NERVE STIMULATION ON POST-HERPETIC NEURALGIA

By

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CHAPTER I
INTRODUCTION

Postherpetic neuralgia (PHN) is defined as a neuropathic pain (NP) that continues from months to years after the cure of the herpes zoster (HZ) infection (1).

Herpes zoster is commonly known as shingles. It is a viral disease caused by reactivation of varicella-zoster virus which remains dormant in the sensory ganglia of the cranial nerve or the dorsal root ganglia after a previous varicella infection. Varicella is commonly known as chickenpox; it occurs in children while herpes zoster occurs in adults or the elderly. It is believed that zoster occurs due to the failure of the immune defense system to control the latent replication of the virus. The incidence of herpes zoster is strongly correlated to the immune status. Individuals who maintain a high level of immunity rarely develop shingles. The infection is not benign and can present in many ways. Even after herpes zoster resolves, many patients continue to suffer from moderate to severe pain known as postherpetic neuralgia (2).

The PHN is the main prevalent HZ complication. The incidence of PHN is 10% in people > 40 years old, 20%-50% of people > 60 years old, and scarcely reported in people < 30 years old and it enhances with increased age and reduced immunity. Consequently, it was mainly reported in the elders (1).

PHN is the most common long-term complication of varicella-zoster virus (VZV) reactivation, also known as human herpesvirus-3 (HHV-3). This reactivation of the dormant VZV is known as herpes zoster or shingles. VZV is the causative agent for the childhood condition varicella, colloquially known as chickenpox (3).

Pain in PHN is described as burning, throbbing, lancinating, or electric-shock-like, and intermittent or continuous. PHN is sometimes associated with allodynia or hyperesthesia, spreading at the same dermatome(s) as in HZ (4).

For a 1-year incidence cohort of people with shingles in the UK, the lifetime costs of treating PHN are between 4.8 million British pounds sterling (incidence of 21 000 people) and 17.9 million British pounds sterling (incidence of 78 200 people) (5).

The pain and discomfort associated with herpes zoster can be prolonged and disabling, diminishing the patient's quality of life and ability to function to a degree comparable to that in diseases such as congestive heart failure, myocardial infarction, diabetes mellitus type 2, and major depression (6).

The treatment of PHN is a challenge and should include drugs such as anticonvulsants like pregabalin and gabapentin, tricyclic antidepressants such as nortriptyline, and amitriptyline, topical lidocaine, topical capsaicin, opioids, and botulinum toxin. The PHN is often resistant to traditional analgesic therapies. Presently, no drug can cure it completely and definitively. The treatment regimens used for relieving PHN give only transient pain relief and some are ineffective at all. Furthermore, these drugs have severe adverse effects and some can result in severe disability to the patients (1).

Transcutaneous auricular vagus nerve stimulation (taVNS) is a non-invasive brain stimulation technique that involves the delivery of electrical stimulation to the auricular branch of the vagus nerve (ABVN) accessible through the skin of the outer ear (7). this stimulation of the vagal auricular branch leads to autonomic regulation and reduced inflammation (8).

In 2000, inspired by VNS, auricular acupuncture to treat epilepsy, and the distribution of the ABVN in the concha, Enrique Ventureyra formally proposed the concept of transcutaneous VNS for the first time (9).

The vagus nerve is the main nerve of the parasympathetic autonomic nervous system. Beyond its vegetative functions, the vagus nerve possesses anti-inflammatory and analgesic properties (10).

Vagus nerve stimulation (VNS) is US Food and Drug Administration (FDA) approved for use in the treatment of epilepsy and depression in patients aged >12 years and is currently being explored as treatment for a variety of other autoimmune and chronic inflammatory disorders, due to its demonstrated anti-inflammatory properties (11).

Anatomical research shows that the only branch of the VN that reaches the body surface is the auricular branch of the VN (ABVN). The ABVN is mainly distributed in the concha (cymba conchae and cavum conchae), and the cymba conchae is supplied exclusively by the ABVN. The afferent fibers of the ABVN enter the vagal trunk through the jugular ganglion and project to the nucleus of the solitary tract (NTS), where the central integration of autonomic neurons occurs. It collects afferent information and activates the caudal ventrolateral medulla and dorsal motor nucleus to regulate central autonomic activity (12).

As an emerging neuromodulation therapy, transcutaneous auricular vagus nerve stimulation (taVNS) has been proven to be safe and effective for epilepsy, major depressive disorders, insomnia, glucose metabolic disorders, pain, stroke, post stroke rehabilitation, anxiety, fear, cognitive impairment, cardiovascular disorders, tinnitus, Prader-Willi Syndrome, and COVID-19(13).

Statement of problem:

Does the application of transcutaneous auricular vagus nerve stimulation (taVNS) help in minimizing pain of Postherpetic neuralgia (PHN)?

Purpose of the study:

The purpose of this study is to evaluate the therapeutic efficacy of transcutaneous auricular vagus nerve stimulation (taVNS) in the treatment of patients with post-herpetic neuralgia (PHN).

Significance of the study:

The pain associated with Postherpetic neuralgia (PHN) can be unbearable, impacting physical, psychological, and social aspects of life. It places a significant burden on patients, healthcare professionals, and institutions in terms of both suffering and costs. Medications (such as tricyclic antidepressant "TCAs", pregabalin, gabapentin, and 5% lidocaine) are commonly used for PHN. However, medication has limitations, including the need for monitoring adverse effects in the elderly and those with impaired visceral function. Gradual titration to the optimal dose can also affect patient adherence (14).

Postherpetic neuralgia (PHN) poses a dual challenge: it significantly reduces patients' quality of life and places a burden on the healthcare system. Despite recommendations for zoster vaccination in older adults, PHN remains prevalent.

Investigating novel treatments is essential to alleviate suffering, enhance patient care, and reduce the overall impact of this condition.

Transcutaneous auricular vagus nerve stimulation (taVNS) as a non-invasive approach could offer an alternative or adjunctive therapy for PHN patients, potentially reducing reliance on medications and invasive procedures.

Understanding the impact of taVNS on PHN may open new avenues for pain management and improve the daily lives of those affected.

Furthermore, there is a lack in the quantitative knowledge and information in the published studies about efficacy of taVNS on PHN.

So, this study is designed to outline the therapeutic efficacy of taVNS on the PHN.

Delimitation:

1. Subjects:

Thirty-four male and female patients diagnosed with PHN with age ranging from 35 to 65 years old and will be randomly allocated into two equal groups; each one has 17 patients.

• Group (A): Study group (this group will receive taVNS in addition to traditional medical treatment).

• Group (B): Control group (this group will receive the same traditional medical treatment only).

2.Equipment and tools:

2.1. Measurement equipment:

- Brief Pain Inventory (BPI) short form.
- Short form McGill pain questionnaire 2 (SF-MPQ-2).

2.2. Therapeutic equipment and tools:

- EV-906 device (has the criteria of ISO 13485; QSR (US FDA) as well as CE (93/42/EEC/MDD).
- TENS Ear Clips for Vagus Nerve Stimulation (ASIN: B0C1GB3B1Q).

Basic Assumption:

It will be assumed that:

- Random allocation of participants in both groups.
- All information from patients will be correct.
- All patients will follow the instructions during the treatment.
- All patients will receive the same kinds of medical, nursing care in both groups.
- All subjects will continue in the study.
- Physiological and psychological variations will not affect the study.
- Participants in the active taVNS group receive consistent stimulation parameters (frequency, intensity, duration).
- Validated outcome measures (e.g., pain intensity, quality of life) should reliably capture relevant aspects of PHN.
- Participants understand the study's purpose, risks, and benefits.
- Long-term follow-up (e.g., 3 months, 6 months) assesses sustained effects.
- Participants adhere to the assigned treatment (active or sham).
- Valid statistical methods to yield meaningful results.
- Findings from the RCT apply to the broader PHN population.
- Patient will be free from any other dysfunctions except PHN.

Hypothesis:

It will be hypothesized that:

Transcutaneous auricular vagus nerve stimulation (taVNS) has no therapeutic effect on Postherpetic neuralgia (PHN).

Definition of Terms

The following terms will be defined for the clear understanding of the terminology used in the present study:

Neuralgia:

The neuralgias are characterized by pain in the distribution of a cranial or cervical nerve. While most often brief, severe, and paroxysmal, continuous neuropathic pain may occur. The most commonly encountered entities include trigeminal, postherpetic, glossopharyngeal, and occipital neuralgia. More unusual cranial neuralgias may occur in periorbital (e.g., supraorbital neuralgia) and auricular (e.g., nervus intermedius neuralgia) distributions (15).

Pain:

The current International Association for the Study of Pain (IASP) definition of pain as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" was recommended by the Subcommittee on Taxonomy and adopted by the IASP Council in 1979(16).

Postherpetic neuralgia (PHN):

Postherpetic neuralgia (PHN) is a chronic painful sequela of peripheral sensory nerve injury following acute shingles, which in turn is the result of the reactivation of herpes zoster (HZ) in the dorsal root ganglia (DRG) of the affected nerves. In addition to the pain of PHN, which is one of the most easily recognized types of neuropathic pain, patients with this chronic painful disorder also experience other sequelae, such as a variable degree of sensory loss and paresthesia in the

distribution of the affected nerve roots, all of which reflect the underlying pathology and pathophysiological mechanisms (17).

Transcutaneous auricular vagus nerve stimulation (taVNS):

Transcutaneous auricular vagus nerve stimulation (TaVNS) is a non-invasive external stimulation (of the auricular branch of the vagus nerve) and seems to be an interesting alternative. Good tolerability and effectiveness have been demonstrated for taVNS (18).

CHAPTER II
REVIEW OF RELATED LITERATURES

The literature review will present relevant studies and literature related to the central concept of this study, organized under the following headings:

1.Postherpetic neuralgia (PHN):

1.1. Background.

1.2. HZ and PHN pathophysiology and clinical presentation.

1.3. Modalities in managing PHN.

2. Transcutaneous auricular vagus nerve stimulation (taVNS):

2.1. Background.

2.2. Related anatomy.

2.3. Vagus nerve, inflammatory response and autonomic balance.

2.4. TaVNS mechanism of action.

2.5. Clinical applications of taVNS.

2.6. Side effects and contraindications of taVNS.

2.7. Types of nervous fibers and stimulation parameters.

1.Postherpetic neuralgia (PHN):

1.1. Background:

Postherpetic neuralgia (PHN) is one of the most common debilitating complications of herpes zoster (HZ). Although PHN has been defined in various ways, it is generally agreed that the transition from HZ to PHN occurs when pain in the area affected by HZ persists ≥3 months after crusting of the skin lesions. PHN

pain may lead to depression, fatigue, insomnia, altered activities of daily living, and decreased socialization. Individuals may also experience anorexia, physical inactivity, and difficulty concentrating. Treatment for pain is often initiated at the time of rash onset and may be necessary for months to years. However, the effectiveness of available treatments varies. In some patients, PHN may persist for years and can be refractory to treatment. (19).

A product of re-activation of the Varicella-Zoster virus (VZV), HZ is diagnosed more than 1 million times annually in the United States. Approximately 20% of patients with HZ will experience PHN and will continue to suffer intermittent neuropathic symptoms, including itching and pain, that is sharp, stabbing, throbbing or burning, with the pain localized to the site of their original rash (20).

Post-herpetic neuralgia (PHN) has a long and intriguing history, interwoven with the understanding of shingles itself. the Ebers Papyrus (1550 BC) from Egypt mentions a blistering skin condition with associated discomfort, potentially referring to shingles and PHN (21).

The connection between shingles and PHN becomes increasingly recognized by physicians. In 1832, Robert Willan, an English physician, described the characteristic features of PHN and its association with shingles in his book, "On Cutaneous Diseases" (22).

1.2. HZ and PHN pathophysiology and clinical presentation:

The pathophysiology of PHN is poorly understood. However, it is certain that HZ affects the central and peripheral nervous systems, which can subsequently lead to the occurrence of PHN. Two main processes play roles in the development of

PHN: sensitization and deafferentation. After resolution of the primary infection of VZV, replication of latent VZV in the sensory ganglia leads to inflammatory neural damage, resulting in acute zoster pain and PHN. Sometimes motor paresis may occur due to the spread of infection and inflammation from the dorsal horn to the anterior horn. During the course of HZ, both the peripheral and central nervous systems can be injured. In skin biopsies taken from patients with PHN, severe depletion of epidermal free nerve endings was found in the involved areas. In addition, in an autopsy study of the spinal nerves of patients who had experienced HZ, atrophy of the DRG was found only in the patients with PHN. Previous research found increases in the subtype of voltage-gated sodium channels, alteration of voltage-gated potassium channels, and increases in transient receptor potential vanilloid 1 (TRPV1) in animal studies of a neuropathic pain model. In addition, the loss of γ-aminobutyric acid (GABA) inhibitory neurons in the DRG after nerve injury causes loss of descending inhibition, leading to excessive reaction of nociceptive neurons of the spinal DRG (23).

Advancing age is the most common risk factor for herpes zoster. Other risk factors include exposure to VZV in utero or before age 1 year, patients with immunocompromised states or who take immunosuppressants, and other conditions that can lower a patient's immunity, such as being a recipient of hematopoietic stem-cell transplants or organ transplants, psychological stress, and physical trauma (24).

The inflammatory mediators released from injured tissue, including substance P, bradykinin, histamine, cytokines, and ions (K+, H+) activate peripheral nociceptors directly by lowering the threshold of nociceptors, leading to peripheral sensitization. These changes also increase the ectopic discharge rate of C-fiber nociceptors. Thus, repetitive discharge of C-fibers can lead to a prolonged response of neurons in the DRG, which contributes to central sensitization. Therefore,

sensitization of the peripheral and/or central nervous systems produces spontaneous pain, allodynia, and hyperalgesia. The allodynia and sensory loss in the affected dermatomes are associated with deafferentation, which results in dorsal horn reorganization. The decreased number of C-fibers of the peripheral nerves, in combination with deafferentation, induces sprouting of Aβ-fibers, which normally transmit innocuous touch and pressure. Aβ-fiber rewiring in the DRG, which connects with the pain-transmitting spinothalamic tracts, produces dynamic and tactile allodynia (23).

Zoster is often followed by chronic pain (postherpetic neuralgia) as well as meningitis or meningoencephalitis, cerebellitis, isolated cranial nerve palsies that produce ophthalmoplegia or the Ramsay Hunt syndrome (RHS), multiple cranial nerve palsies (polyneuritis cranialis), vasculopathy, myelopathy and various inflammatory disorders of the eye, the most common of which is progressive outer retinal necrosis (PORN). Importantly, VZV reactivation can produce chronic radicular pain without rash (zoster sine herpete), as well as all the neurological disorders listed above without rash. It was assumed that "while zoster is typically diagnosed through clinical observation, all neurological complications resulting from VZV reactivation without a rash necessitate confirmation through virological testing. Notably, the most informative tests involve detecting VZV DNA or anti-VZV IgG antibodies in cerebrospinal fluid (CSF) (25)."

The differential diagnosis for HZ includes herpes simplex virus, impetigo, candidiasis, contact dermatitis, insect bites, autoimmune blistering disease, dermatitis herpetiformis, and drug eruptions (26).

PHN occurs in the same dermatomes as the HZ rash, and stems from damage to peripheral and central neurons that may be a byproduct of the immune/inflammatory response that accompanied VZV reactivation and migration.

When damaged, peripheral and central nerve fibers may develop a lower threshold for action potentials, discharge spontaneously, and exhibit disproportionate responses to stimuli, resulting in peripheral sensitization and pain without painful stimuli (allodynia). Patients with PHN experience three major types of pain: 1) constant pain without a stimulus (often described as burning, aching, or throbbing), 2) intermittent pain without a stimulus (often described as stabbing, shooting, or electric shock-like), and 3) pain brought on by a stimulus but is disproportionate to the stimulus (hyperalgesia), enduring for at least 3 months after healing of the HZ-related skin rash. Pain intensity and quality should be assessed using an appropriate pain scale, based on the patient's ability to communicate – a numerical rating scale (usually an 11-point scale: from 0, no pain, to 10, severe pain), a visual analog scale, or verbal descriptor scale (e.g., McGill Pain Questionnaire) (27).

The intensity of pain associated with herpes zoster can also be assessed using ZBPI (the zoster brief pain inventory) (28).

In addition, patients may experience a variety of abnormal sensations (dysesthesias or paresthesia). Patients with PHN report decreased quality of life and interference with activities of daily living that may affect physical, psychological, and social aspects of their lives as well as their ability to function (27).

1.3. Modalities in managing PHN:

PHN interferes with the patient's daily activities, such as dressing, bathing, eating, shopping, and traveling, leading to a reduced quality of life, psychological stress, and physical disabilities. The current treatment options and new developments in the treatment of PHN are summarized in this fig.1 (29).

First Line Agents [14]	Anticonvulsants: Gabapentin Pregabalin	Antidepressants: Nortriptyline, desipramine, (amitriptyline, imipramine)
Second Line Agents [14]	Topical lidocaine Topical capsaicin Tramadol Reason for them being second line is a low quality of evidence (lidocaine), a relatively small effect size (topical capsaicin), or lower tolerability or safety (tramadol). Topical agents can be used at any time for focal pain	
Third Line Agents [14]	Opioids Botulinum Toxin A	
Invasive or Non-invasive Methods	Nerve blocks Neuromodulation Nerve stimulation Radiofrequency Scrambler therapy	
Combination Therapy	Various combination of above treatments are used to provide pain relief to patients	

Figure 1:Treatment Summary for Postherpetic Neuralgia.

Post-herpetic neuralgia (PHN) is common and treatment is often suboptimal with less than half of patients achieving adequate 50% pain relief. As an area of unmet clinical need and as an archetype of neuropathic pain, it deserves the attention of clinicians and researchers (30).

2. Transcutaneous auricular vagus nerve stimulation (taVNS):

2.1. Background:

Transcutaneous auricular vagus nerve stimulation (taVNS) is a rapidly developing technique for non-invasive neuromodulation that was repeatedly used to both improve health and mitigate health burden. While the stimulators were initially implanted invasively, they are increasingly replaced by non-invasive stimulators which first studies used to treat neurological and psychiatric disorders with. The non-invasive, transcutaneous stimulation of the auricular branch of the vagus nerve activates the nucleus tractus solitarii. This brainstem activation leads to a broad distribution of afferent information within several cortical and subcortical areas, including the serotonergic raphe nuclei, the cholinergic nucleus basalis Meynert, the pedunculopontine nucleus, and the noradrenergic locus coeruleus (31). The nucleus

of the solitary tract receives approximately 95% of projections from the vagus nerve (32)

Although it is generally known that the ear is the auditory organ, there is a long history of exploring its connection with the rest of the body and treating diseases by stimulating the external ear, both in the Eastern and Western medicine. The auricle's importance was noted in Huang Di Nei Jing (Internal Classic of the Yellow Emperor), a classic in traditional Chinese medicine compiled around 500 BC. In this book, the ear is closely associated with the meridians. Hippocrates used the method of pricking the dorsal auricular vein to treat impotence in the 4th century BC. The Egyptologist Alexandre Varille (1909–1951) recorded that ancient Egyptian women would insert needles or cause heat burns to the outer ear if they did not want to have any more children. In the subsequent two thousand years, with the exchange between Eastern and Western civilizations, more and more diseases were treated by traumatic stimulation of the outer ear, such as cauterization, cutting, and pricking. However, there was no systematic theoretical explanation for this treatment until 1832, when Friedrich Arnold first described the Arnold reflex. Since then, researchers have reported various reflexes and phenomena of a connection between the external ear and the viscera, and gradually opened up discussion of the connection between the external ear and the VN. The term of transcutaneous VN stimulation was coined 20 years ago, and research on this method has gradually increased (fig.2) (12).

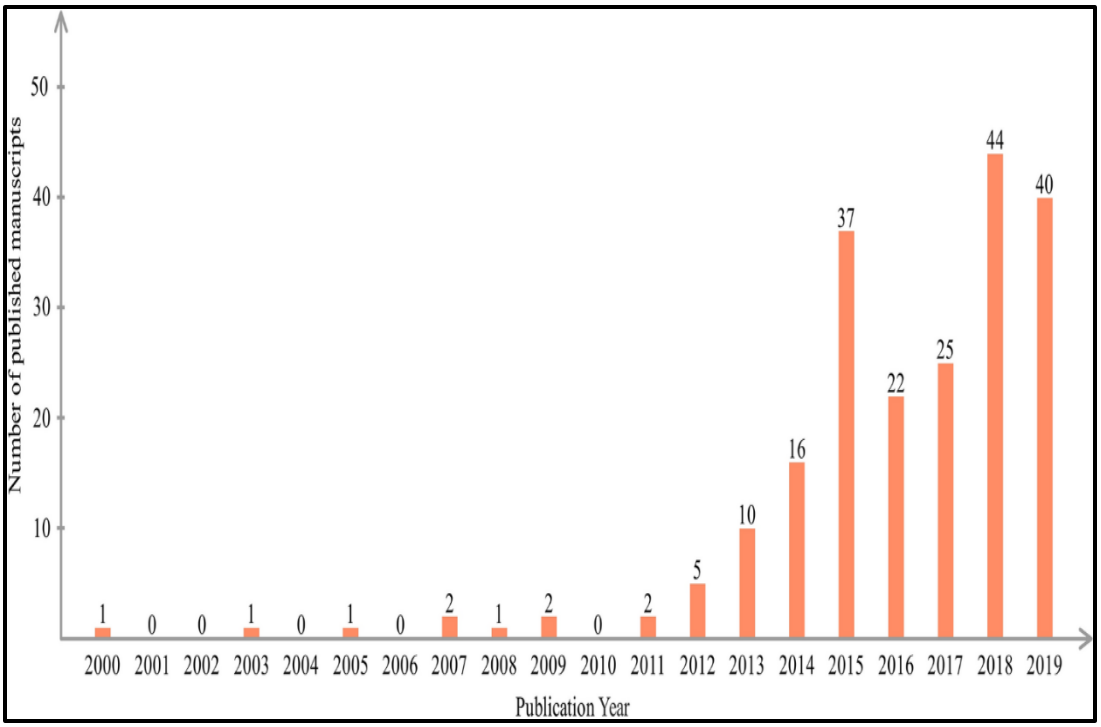


Figure 2: Numbers of publications on taVNS from 2000 to 2019.

2.2. Related anatomy:

The vagus nerve has its origin in the medulla oblongata and exits the skull via the jugular foramen. There are two ganglia on the vagus nerve (superior and inferior) as it exits the jugular foramen; the spinal accessory nerve (CN XI) joins the vagus nerve just distal to the inferior ganglion (fig.3) (33,34).

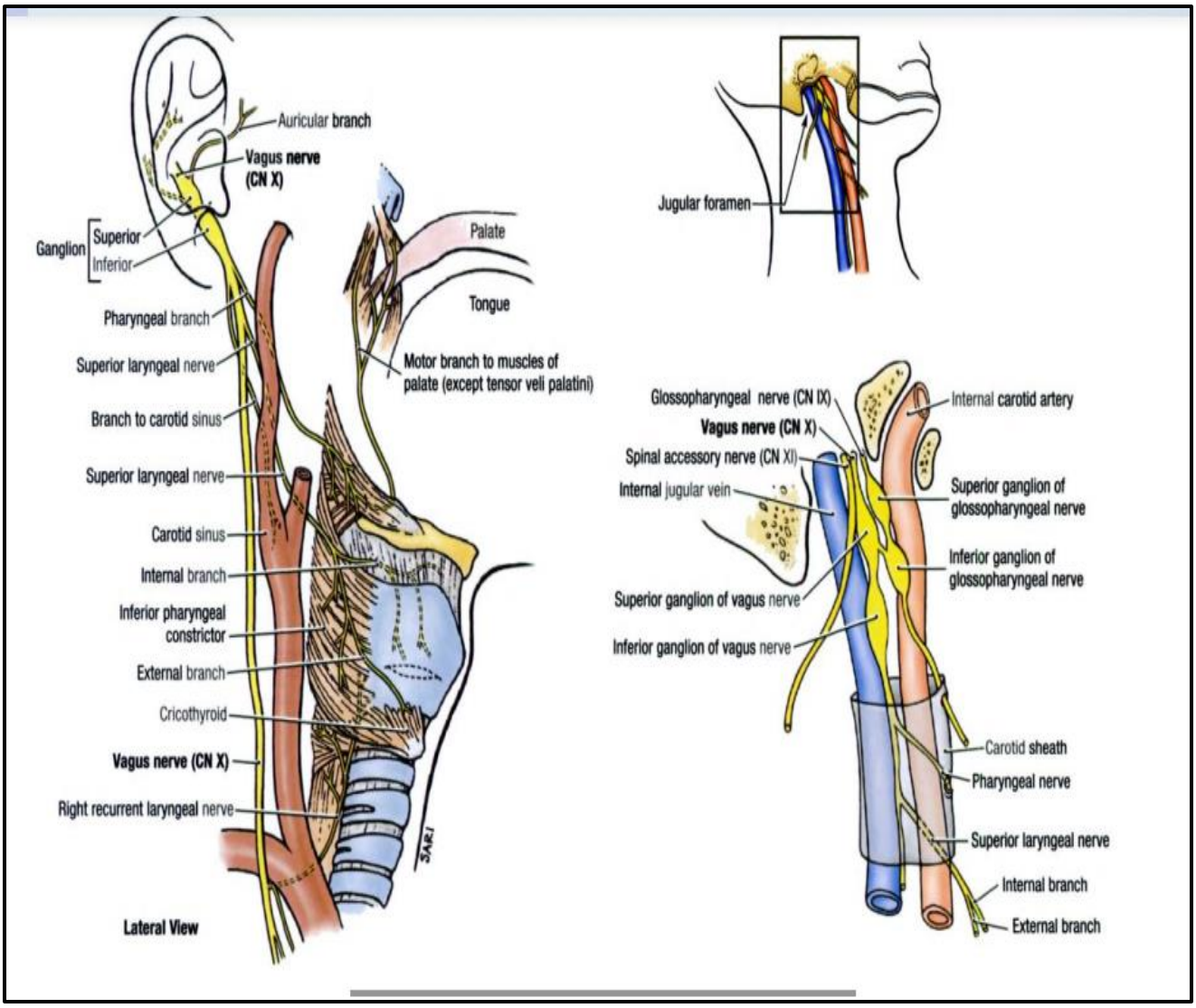


Figure 3:vagus nerve anatomy.

The vagal nucleus consists of four nuclei located in the medulla oblongata. The three main nuclei are the dorsal motor nucleus of the vagus nerve (cranial nerve [CN] X), nucleus ambiguus, and the solitary nucleus. The fourth nucleus has a minor input from the vagus nerve, the spinal trigeminal nucleus, which receives the main input from the trigeminal nerve (35).

The Auricular Branch (ramus auricularis; nerve of Arnold) arises from the jugular ganglion, and is joined soon after its origin by a filament from the petrous ganglion of the glossopharyngeal; it passes behind the internal jugular vein, and

enters the mastoid canaliculus on the lateral wall of the jugular fossa. Traversing the substance of the temporal bone, it crosses the facial canal about 4 mm. above the stylomastoid foramen, and here it gives off an ascending branch which joins the facial nerve. The nerve reaches the surface by passing through the tympanomastoid fissure between the mastoid process and the tympanic part of the temporal bone, and divides into two branches: one joins the posterior auricular nerve, the other is distributed to the skin of the back of the auricula and to the posterior part of the external acoustic meatus (36).

The ABVN innervates the central region of the auricle: the concha (upper and lower), much of the antihelix, and the internal portion of the tragus(fig.4) (32,37).

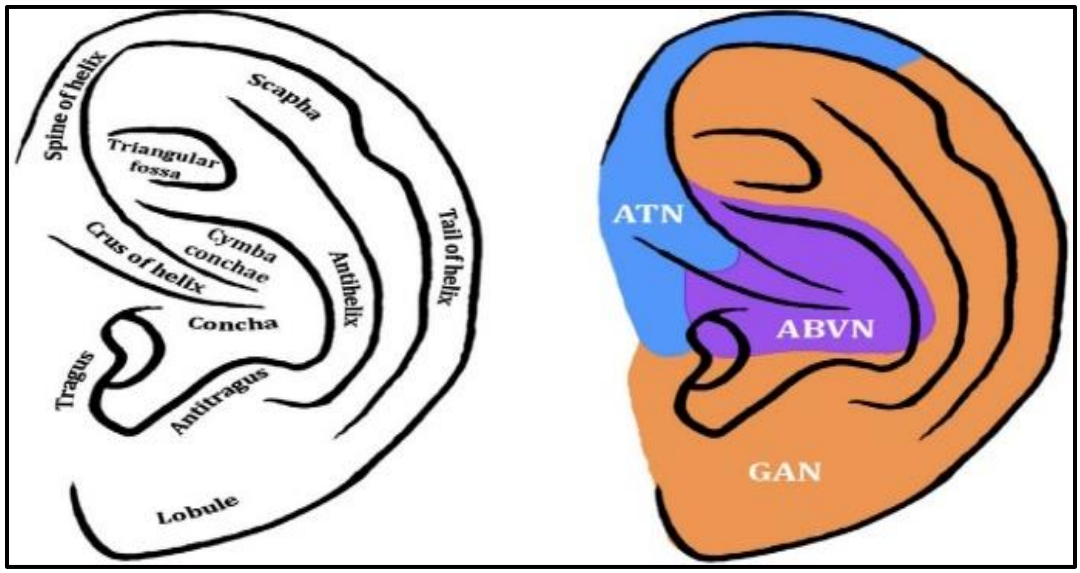


Figure 4: Diagram of the external ear and its hypothesized cutaneous innervation.

The vagus nerve contains three fiber types: highly myelinated A fibers, which have low activation thresholds; lightly myelinated B fibers; and unmyelinated C fibers, which have high activation thresholds. The B and C fibers have been implicated in regulation of heart rate ; no specific function has been attributed to the vagal A fibers, but our recent results suggest that the A fibers may contribute to the regulation of cytokine release(38).

Myelinated axons in the left and right ABVN averaged to 385 and 363, respectively. Numbers of A beta axons measuring ≥7 μm averaged to 64 and 78 on the left and right, respectively. The ratio of A beta axons in the ABVN and CVN was ~1:5 and 1:6 on the left and right side, respectively so transcutaneous ABVN stimulation might be a promising alternative to invasive CVN stimulation (39).

2.3. Vagus nerve, inflammatory response and autonomic balance:

The vagus nerve (10th cranial pair) is the largest and most important nerve in the parasympathetic nervous system and modulates the immune response to inflammatory processes that occur in our body. It is composed of sensory (»80%) and motor fibers. Inflammatory mediators released due to any aggression (e.g., pro-inflammatory cytokines) activate vagal afferent fibers that convey information to the nucleus of the solitary tract (NST). Activation of NST neurons originates the anti-inflammatory response in the following two different ways. In the first, known as the hypothalamic-pituitary adrenal axis (HPAA), NST efferents to the paraventricular nucleus of the hypothalamus stimulate the release of corticotropin-releasing hormone (CRH), which stimulates the secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland. ACTH reaches the adrenal gland, stimulating the production of glucocorticoids, which act on the spleen leading to reduction of cytokine release. In the second way, known as "cholinergic anti-inflammatory reflex," NST efferents activate the dorsal motor nucleus of the vagus nerve (DMNV), and its cholinergic motoneurons project to the splenic nerve in the celiac ganglion, releasing acetylcholine (ACh) in the preganglionic terminals and provoking release of norepinephrine (NE) in the spleen, which ultimately inhibits macrophages' cytokines release, decreasing inflammation. cholinergic anti-inflammatory reflex illustrated in **figure** 5 (37).

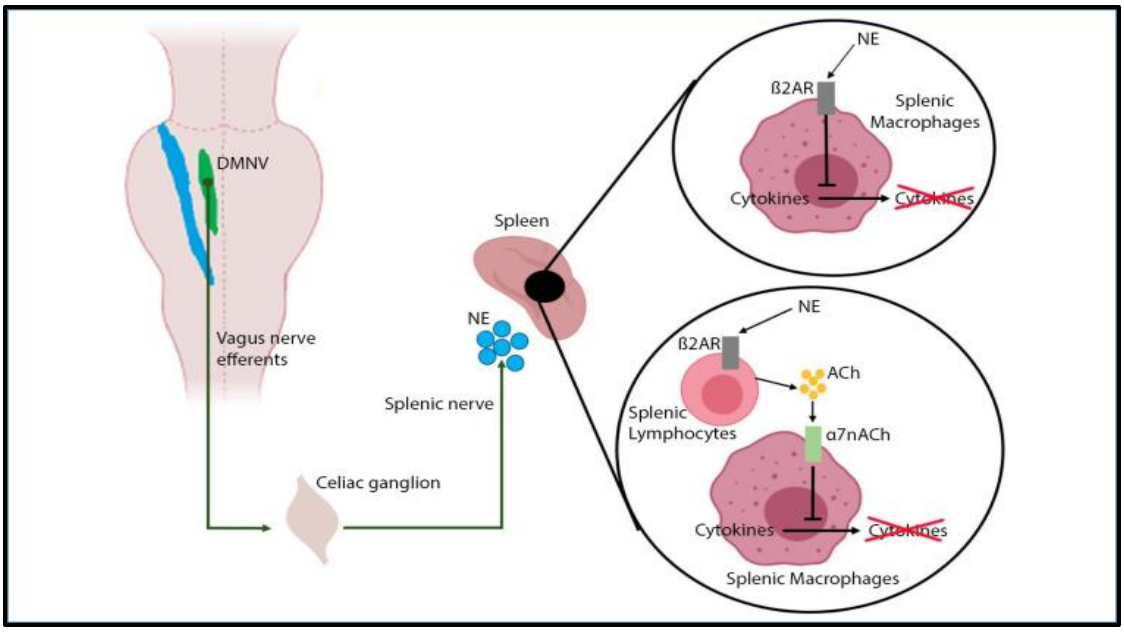


Figure 5: Scheme of the anti-inflammatory activity of the vagal efferents.

2.4. TaVNS mechanism of action:

According to Neurochemical Effects and Pathophysiologic Implications of Vagus-Nerve Stimulation it was submitted that "The vagus nerve primarily projects to the NST. In the NST, the nerve releases various neurotransmitters, including: Glutamate, Aspartate, GABA, Acetylcholine and Other neuropeptides. VNS leads to a long-lasting increase in noradrenaline release in several brain regions: Basolateral amygdala, Thalamus, Hippocampus, Neocortex. This effect is likely mediated by the LC (Locus Coeruleus) or a direct projection from the A2 cell group of the NST to the LC. Experimental evidence links these structures and noradrenaline to the antiseizure and antidepressant effects of VNS, Not only does VNS increase levels of free GABA in cerebrospinal fluid and the hippocampus, but it also decreases glutamate and increases GABA in the NST. These effects contribute to the seizure-attenuating effects of VNS. As the NST projects to the DRN (Dorsal Raphe Nucleus), a major source of serotoninergic innervation in the brain, VNS may

modulate mood, anxiety, and other neuropsychiatric disorders via this pathway. In another pathway VNS increases neurotrophic factors in the hippocampus and neocortex, this action may be implicated in VNS' antidepressant effect. Additionally, VNS can stimulate c-Fos transcription, cellular proliferation, and neurogenesis in the hippocampus, these effects are associated with VNS' impact on neuronal plasticity, memory, learning, mood, and cognitive processes. Recently some studies demonstrate that VNS modulates the release of various factors, including nitric oxide, melanocortin, inflammation, and glutamate excitotoxicity. Finally, VNS exerts an anti-inflammatory effect by suppressing cytokine production via the cholinergic anti-inflammatory pathway" (40).

TaVNS induces the cholinergic anti-inflammatory pathway (CAP) through stimulation of the ABVN, which is directly connected to the NTS. The NTS serves as the endpoint for the afferent fibers of the vagus nerve and is recognized as a relay station for visceral sensation. It plays a crucial role in receiving signals from the ear and adjusting various bodily functions. The NTS can project directly or indirectly from bottom to top to many nuclei such as the parabrachial nucleus, dorsal raphe nucleus, locus ceruleus, hypothalamus, thalamus, amygdala, and hippocampus. **Figure** 6 illustrating Potential mechanism of taVNS, A) The external ear and its hypothesized cutaneous innervation by the ABVN. B) Modulation of brain networks mainly depend on the extensive fibrous connections formed by ABVN projections to multiple brain regions through the NTS to regulate neuroendocrine, emotional, and cognitive functions. C)The balance of the production of cytokines depends on the wiring of CAP (12).

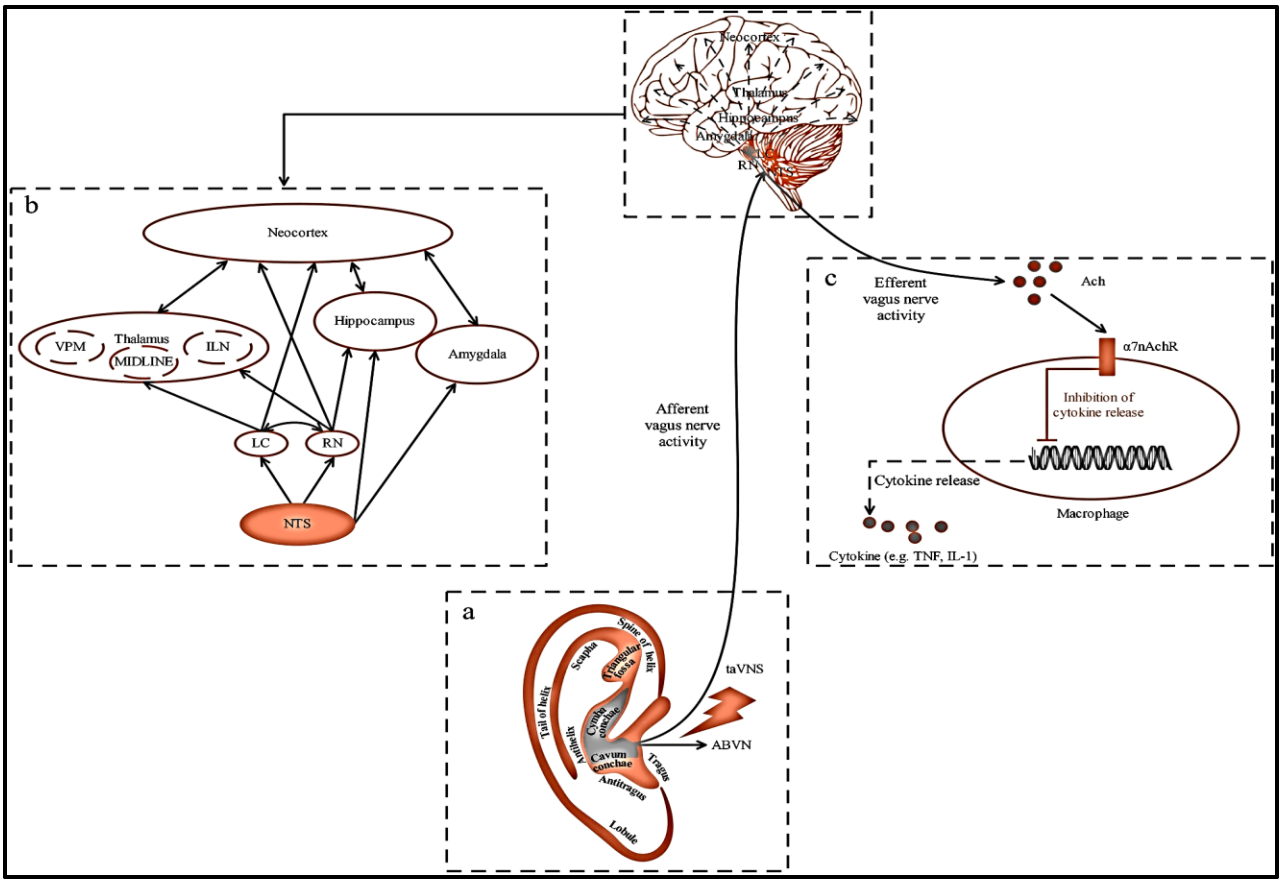


Figure 6: Potential mechanism of taVNS

2.5. Clinical applications of taVNS:

- Imbalances in ANS activity have been linked to many clinical disorders, including heart failure, inflammatory bowel disease, and chronic pain syndromes. In general, reported imbalances involve elevated sympathetic activity associated with a deficit in parasympathetic activity. VNS corrects autonomic imbalance and increases parasympathetic activity (37).
- According to taVNS mechanism It can be argued that "taVNS is effective treatment for: A- Brain Diseases such as Epilepsy, depression and disorders of consciousness (DOCs). B- cardiovascular diseases such as arrhythmias caused by myocardial ischemia. C-Digestive system Diseases such as intestinal inflammation, postoperative ileus (POI) and colon cancer induced

by 1-dimethylhydrazine (DMH)by the cholinergic anti-inflammatory pathway" (12).

- Transcutaneous vagus nerve stimulation (tVNS), if combined with sound therapy (ST), reduces the severity of tinnitus and tinnitus-associated distress (41).
- Treatment of chronic migraine by t-VNS at 1 Hz was safe and effective (42).
- Effect of auricular transcutaneous electrical nerve stimulation on pain threshold was found to be increased by over 50% of its pretreatment baseline (43).
- Clear antinociceptive effect of VNS in models of acute or inflammatory pain with different stimulation protocols including the one used in epileptic patients (44).
- Transcutaneous vagal nerve stimulation may produce both anti- and pro-nociceptive effects in healthy volunteers (45).
- TaVNS can increase of mechanical and pressure pain threshold and a reduction of mechanical pain sensitivity (46).

2.6. Side effects and contraindications of taVNS:

Auricular vagus nerve stimulation (aVNS) is safe, with minor side effects such as headache, dizziness, skin irritation, or pain. Surface electrodes are used in transcutaneous aVNS (taVNS), making the stimulation not as selective and precise as when using miniature needles, which can contribute to a lower effectiveness of the technique and a higher incidence of side effects. Very mild adverse effects of aVNS have been reported and observed in a few cases: Arnold's cough reflex, vasovagal reflex, tearing, and bradycardia, all of which are indirect effects of afferent-efferent vagal reflexes. Furthermore, it is known that stimulation of

cholinergic nerves can cause bronchial spasm and increase mucus production in the airways, which could attenuate the beneficial effects of aVNS in the anti-inflammatory process. Fortunately, these are all very rare side effects, occurring in less than 1% of the patients, and are widely overcome by the potential advantages of aVNS, in view of severity of comorbidities in COVID-19 patients. taVNS is contraindicated in people with vagal hypersensitivity, hemophilia, psoriasis vulgaris at the application site, and patients with active implantable devices, such as pacemakers, because of their possible interference with the pacing device (37).

2.7. Types of nervous fibers and stimulation parameters:

A tingling sensation should be targeted, as pointed out by some studies. This is because the non-painful stimulus of ABVN would recruit more of the myelinated Aβ fibers in the ear, responsible for mechanoreception and touch sensation, and not the Aδ fibers, responsible for the sensation of pain and temperature. As already mentioned, thicker Aβ fibers are more easily recruitable than smaller Aδ fibers. For this effect to be obtained, the stimulus must be performed with lower current intensities, always below the painful threshold. Another important parameter to optimize the recruitment of Aβ fibers is the stimulation frequency. Slightly higher frequencies, between 20 and 25 Hz, are better for peripheral electrical stimulation of the parasympathetic nervous system, while lower frequencies (between 0.5 and 10 Hz) are better for the sympathetic nervous system. This is because higher frequencies show a shorter duration of the depolarization period and, therefore, are only able to recruit larger and more easily excitable nerve fibers, such as Aβ fibers, which can indirectly modulate the parasympathetic nervous system. On the contrary, more recent studies have shown good results in inflammatory diseases with the use of low frequencies as well, and therefore the ideal frequency has not been established yet (37).

CHAPTER III
SUBJECT, MATERIALS, AND METHODS

In this chapter, we describe the research methodology employed to achieve the study's goals. The chapter is organized under the following headings: subjects, equipment, procedures of the study and the statistical procedures.

1. Subjects:

Sample size calculation was done using pain, as reported in Ing et al study with 95% power at α = 0.05 level, number of measurements 2, for 2 groups and effect size = 0.7 using F-test MANOVA repeated measures within and between interaction (47). The minimum proper sample size is 29 subjects, adding 5 (18%) subjects as drop out, so total sample size is 34 subjects, 17 subjects in each group. The sample size was calculated using the G*Power software (version 3.0.10) (**figure** 7).

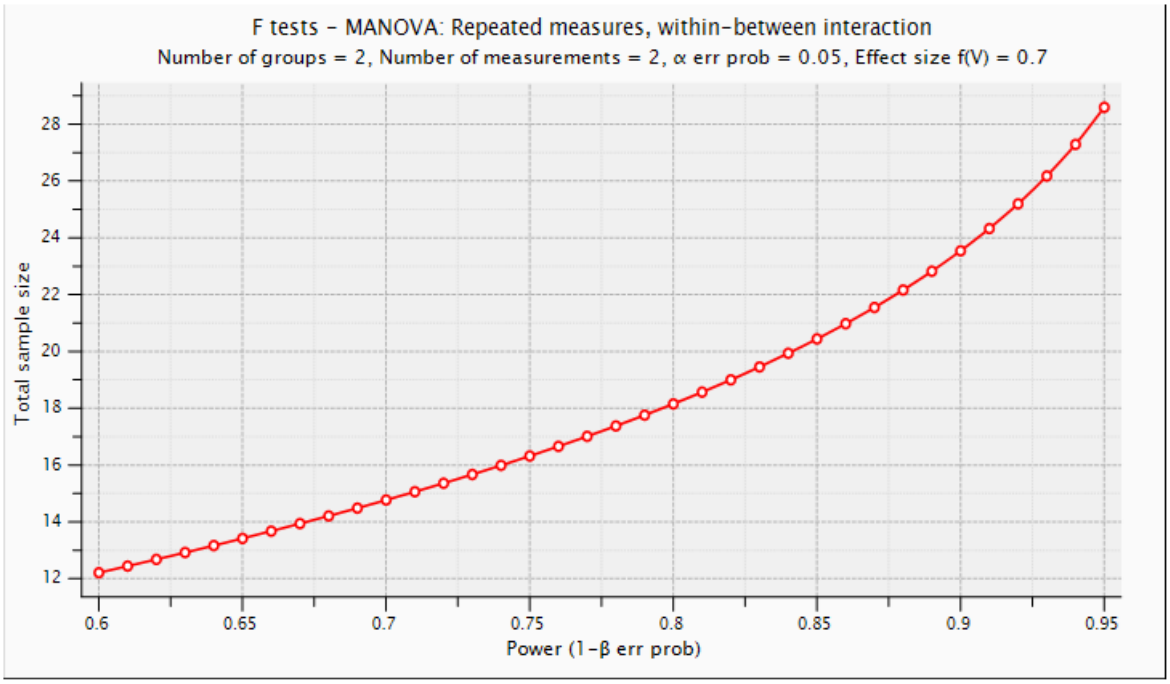


Figure 7:sample size calculation

Thirty-four patients diagnosed with PHN; their age will be between 35 and 65 years old and meet the conditions of inclusion and exclusion criteria (48,55).They will be selected randomly from the pain clinic in Zagazig university hospitals.

1.1. Design of the study:

In this randomised controlled trial study (RCT), the patients will be randomly assigned into two equal groups (17 patients for each group) by using closed envelope method.

1.1.a. Group A (study group):

In this study group, 17 patients diagnosed with Postherpetic Neuralgia (PHN) received traditional treatment and are advised to do physiotherapy sessions in the form of transcutaneous auricular vagus nerve stimulation (taVNS), with three sessions per week for 4 weeks." (12).

1.1.b. Group B (control group):

In this group, 17 patients diagnosed with Postherpetic Neuralgia (PHN) who consulted with a neurologist or dermatologist will receive their traditional medications only. (27).

1.2 Criteria for the patient selection:

The patients' criteria were classified into two main categories:

1.2(a) Inclusion criteria:

The subject selection will be according to the following criteria:

1.Adults (age between 35 and 65 years old) diagnosed with PHN.

2.Persistent pain for at least 3 months after herpes zoster infection.

3.Only patients who signed the informed consent will be included.

1.2.b. Exclusion criteria:

The potential participants will be excluded if they met any of the following criteria:

1.Pateints with Contraindications to taVNS such as:

(a) pregnancy; (b) active implants (*e.g.*, pacemakers, cochlear implants) or brain shunts; (c) previous neurological or psychiatric diagnoses; (d) history of addiction or substance abuse; (e) trauma and/or brain surgery; (f) cardiac disease; (g) acute or chronic use of medications and/or drugs; (h) susceptibility to headaches and seizures (49).

2.Severe cognitive impairment.

3.Other chronic pain conditions.

2. Equipment and tools:

2.1. Measurement tools:

2.1(a) Brief Pain Inventory (BPI) short form (50):

- It will be administered to participants 3 times (before the application of the 1st session and after 2 weeks and after 4 weeks).
- Administration mood will be interview-based.

2.1(b) Short form McGill pain questionnaire 2 (SF-MPQ-2) (51):

- It will be administered to participants as BPI-SF.

2.2. Therapeutic tools:

As part of our study on Post-Herpetic Neuralgia, we employed the EV-906 TENS machine as a therapeutic tool to give specific parameters for TaVNS and "TENS Ear Clips for Vagus Nerve Stimulation".



Figure 8: EV-906 device

2.2(a) EV-906 device (Fig. 8) (has the criteria of ISO 13485; QSR (US FDA) as well as CE (93/42/EEC/MDD).

2.2(b) TENS Ear Clips for Vagus Nerve Stimulation (Fig.9):

Ear-clip at the left cymba concha. (Fig. 10) ASIN: B0C1GB3B1Q (52).



Figure 9: TENS Ear Clips

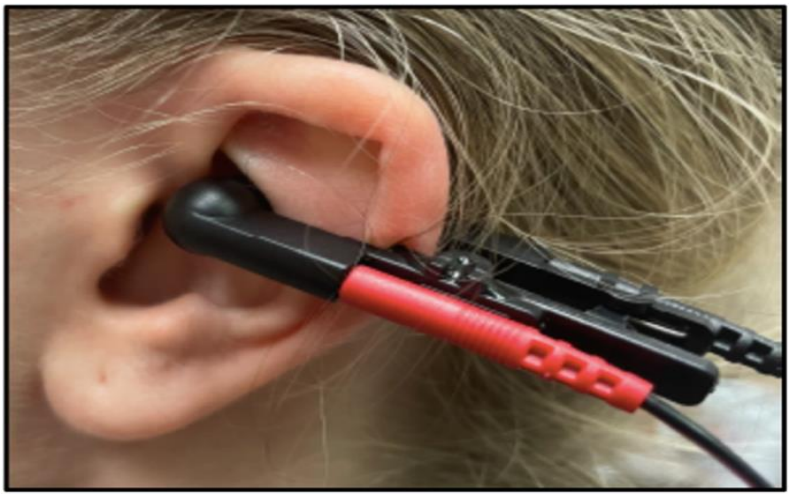


Figure 10: Ear-clip at the left cymba concha

3.Procedure of the study :

- All patients will be informed about the nature and the effect of the treatment and measurement devices.
- The patients will be instructed to report any side effects during the management.

- The procedures of the study will be divided into two main parts:

3.1. Measurement procedures:

These technical procedures will be conducted through two different categories**.**

3.1.(a) Brief Pain Inventory (BPI) short form (53):

➢ Patient data including (name, age, and date of birth) will be recorded in the evaluative sheet.

➢ Patient will be placed in a comfortable position (correct, supine, sideline, and sitting position)

➢ As shown in **appendix A** the Brief Pain Inventory–Short Form (BPI-SF) is a valuable tool for assessing pain severity and its impact on daily functioning. Here are the key measurement procedures involved in using the BPI-SF:

❖ Diagram of Pain Location:

- Patients shade in areas on a diagram where they feel pain.
- They mark an "X" on the area that hurts the most.

❖ Pain Intensity Assessment:

Patients are asked to rate their pain intensity using a 10-point scale for different aspects:

- Worst pain experienced in the last 24 hours.
- Least pain experienced in the last 24 hours.
- Average pain over the same period.
- Current pain level.

❖ Pain Interference Assessment:

Patients rate how much pain interferes with various aspects of their life using the same 10-point scale:

- General activity.
- Mood.
- Walking ability.
- Normal work.
- Relations with other persons.
- Sleep and Enjoyment of life.

3.1.(b) Short form McGill pain questionnaire 2 (SF-MPQ-2) (54).

➢ As shown in **appendix B** for each descriptor, participants should rate the intensity of their pain or symptom using a 0 to 10 scale:

- 0: No pain or symptom described.
- 10: Worst pain imaginable.
- Participants should choose the rating that best reflects their experience during the past week.

➢ All these measurements will be performed to participants 3 times (before the application of the 1st session and after 2 weeks and after 4 weeks).

3.2. Therapeutic Procedures (55):

- This section would be outlined by the following 2 phases:

Phase (1): The Preparatory Treatment Phase.

Phase (2): The Treatment Application Phase.

TaVNS Stimulation will be applied using a portable auricular taVNS device (ev-906 with auricular electrodes) by the following parameters:

Building upon prior research "Stimulation will be delivered continuously for 30 min (pulse width: 250 μs, stimulation frequency: 25 Hz) to the left ear of participants (cymba conchae). Stimulation intensity will be increased gradually from zero to the strongest sensation that the patients could tolerate without pain (approximately 1.5–5 mA, typically between 4 and 6 mA).application will be 3 sessions per week, totally12 treatment sessions in the 4-weeks" (12,31,56,57,58).

The stimulation stimulus will be applied via ear clip electrode, which will be attached to the subject's left ear in cymba conchae; before taVNS will be attached, the skin will be prepared using an alcohol wipe to clean the skin and remove skin particles. Left sided taVNS will be applied to avoid the theoretically possible effect on the heart rate by stimulating vagal parasympathetic fibers (59).

Phase (1): Preparatory treatment phase :

(A) Preparation of patient:

1. The patients will take a comfortable position, seated or laying.
2. The left ear of the participant will be inspected to ensure no jewelry is attached and all make-up and lotion are removed.

3. Confirm there are no skin-related contraindications at the site of stimulation, including sun burn, cuts, lesions, open sores.
4. The skin on and around their left ear will be wiped with alcohol, to eliminate surplus oils to decrease skin resistance and guarantee optimal conductivity.

(B) Preparation of taVNS device and ear electrodes :

1. Ensure that electrodes are disinfected to prevent spread of bacteria between subjects. This can be done using alcohol or sterilization wipes to scrub the electrodes.
2. To ensure safe and effective (taVNS), combine the stimulation electrodes with a conductive medium (such as electrolyte gel or conductive paste). Narrow wooden applicator would be used to create a thin layer (<1 mm) of paste on both electrodes.
3. Connect electrode cables to the stimulation device while the device is turned off and verify the polarity of the electrodes (red/positive electrode: anode, black/negative electrode: cathode).
4. Device Stimulation parameters will be adjusted on 30 min (pulse width: 250 us, stimulation frequency: 25 Hz).

Phase (2): Treatment application phase:

1. After preparing the patient and the ear electrodes, set the device to the taVNS parameters.
2. Clip the spring electrode onto cymba conch point of the left ear such as (**fig**.9).
3. As subjects will feel the pressure of the electrodes clipped to their ear, ensure this pressure is not uncomfortable or disruptive to regional blood flow as demonstrated by pale white skin at clip site or physical pain sensed by the subject.

4. Turn on the device then intensity will be increased gradually according to patient tolerance and inform patient for any side effects.
5. After taVNS When stimulation is completed, record objective data regarding the stimulation discomfort and side effects.
6. Remove the stimulation electrode from the ear and clean residual conductive paste from the subject's ear using an alcohol prep pad.
7. Use alcohol to clean and disinfect the stimulation electrode immediately upon removing from the subject's ear.
8. Inspect the ear for redness or irritation at the stimulation site and record any observations.
9. Session will be repeated 3 time per week for 4 weeks.

4.Statistical procedures:

The collected data will be statistically analyzed using:

- Descriptive statistics (mean and standard deviations).
- Shapiro-Wilk and Kolmogrov-smirnov tests will be used for testing normality of data distribution.
- Inferential statistics; unpaired t-test will be used to compare between the characteristics of the two groups subjects.
- Mixed design MANOVA will be used to compare measured variables between and within groups.
- Statistical analysis will be conducted using SPSS for Windows, version 20 (SPSS, Inc., Chicago, IL). Statistical significance will be set at the ($p< 0.05$).

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Appendix A

1903

Date: (month) / (day) / (year)

Subject's Initials : _____

Study Subject #:

Study Name: _____

Protocol #: _____

PI: _____

Revision: 07/01/06

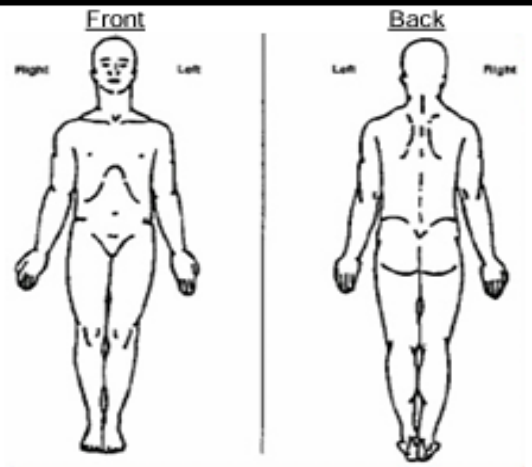
PLEASE USE BLACK INK PEN

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its **worst** in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its **least** in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the **average.**

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have **right now.**

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

Page 1 of 2

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1903

Date: (month) / (day) / (year)

Subject's Initials : _____

Study Subject #:

PLEASE USE BLACK INK PEN

Study Name: _____

Protocol #: _____

PI: _____

Revision: 07/01/05

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
☐ No Relief	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐ Complete Relief

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

B. Mood

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

C. Walking ability

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

E. Relations with other people

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

F. Sleep

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

G. Enjoyment of life

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

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Appendix B

Date: _____

Subject ID: _____

Short-form McGill Pain Questionnaire 2 (SF-MPQ-2)

For this questionnaire, I will provide you a list of words that describe some of the different qualities of pain and related symptoms. Please rate the intensity of each of the pain and related symptoms you felt during the past week on 0 to 10 scale, with 0 being no pain and 10 being the worst pain you can imagine. Use 0 if the word does not describe your pain or related symptoms. Limit yourself to a description of the pain related to your surgery or pelvic pain.

1. Throbbing pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
2. Shooting pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
3. Stabbing pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
4. Sharp pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
5. Cramping pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
6. Gnawing pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
7. Hot-burning pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
8. Aching pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
9. Heavy pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
10. Tender	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
11. Splitting pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
12. Tiring-exhausting	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
13. Sickening	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
14. Fearful	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
15. Punishing-cruel	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
16. Electric-shock pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
17. Cold-freezing pain	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
18. Piercing	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
19. Pain caused by light touch	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
20. Itching	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
21. Tingling or 'pins and needles'	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*
22. Numbness	*none*	0	1	2	3	4	5	6	7	8	9	10	*worst possible*

23. Present Pain Intensity (PPI) – Numerical Pain Rating Scale. On a scale from zero to ten, zero indicating no pain and ten indicating worst pain imaginable, rate your pelvic pain:

None	0	1	2	3	4	5	6	7	8	9	10	*worst possible*

24. Evaluative overall intensity of total pain experience. Please check (√) the word that describes the pain in your pelvic area only.

D *No pain* D *Mild* D *Discomforting* D *Distressing* D *Horrible* D *Excruciating*