CIM
eISSN 2635-9162 / http://chronobiologyinmedicine.org
Chronobiol Med 2019;1(2):51-54 / https://doi.org/10.33069/cim.2019.0011

REVIEW ARTICLE

Therapeutic Application of Transcutaneous Auricular Vagus Nerve Stimulation in Primary Insomnia

Ho-Kyoung Yoon

Department of Psychiatry, Korea University College of Medicine, Korea University Ansan Hospital, Ansan, Korea

Sleep can be considered a highly complex autonomic function. Various conditions disrupting the autonomic nervous system greatly affect sleep and vice versa. Several new brain stimulation methods have become noteworthy therapeutic alternatives to treat various mental disorders. Results from several studies have suggested that vagus nerve stimulation could improve both the clinical symptoms of depression and have an effect on the sleep-wake cycle and sleep microarchitecture. Transcutaneous auricular vagus nerve stimulation is known to be a safe and highly tolerable method and may be a potential alternative treatment for individuals with insomnia. Further studies are needed to determine the potential of this neuromodulation technique for the treatment of insomnia disorders and to elucidate the physiological mechanisms associated with its purported therapeutic effects.

Key Words: Insomnia; Sleep; Vagus nerve stimulation

Received: June 4, 2019 Accepted: June 10, 2019
Corresponding author: Ho-Kyoung Yoon, MD, PhD, Department of Psychiatry, Korea University College of Medicine, Korea University Ansan Hospital, 123 Jeokgeum-ro, Danwon-gu, Ansan 15355, Korea.
Tel: 82-31-412-5140, Fax: 82-31-412-5144, E-mail: hkhkgogo@korea.edu

INTRODUCTION

Insomnia is characterized by difficulty in falling asleep, daytime sleepiness, and an excessively earlier wake-up time than desired, resulting in unsatisfactory sleep quality and quantity [1,2]. Insomnia reduces the function and quality of life during the daytime and increases the risk of physical and mental illness, which can result in social and occupational difficulty and disability [3].

Current medications for insomnia include benzodiazepine receptor agonists, antihistamines, tricyclic antidepressants, and melatonin receptor agonists. However, they are associated with side effects including drowsiness, dizziness, and impaired cognitive function, especially in elderly populations. Therefore, medication use for insomnia requires special attention [4,5]. In addition, non-pharmacological treatment, such as stimulant control therapy, relaxation training, and cognitive behavioral therapy, are often difficult to perform in everyday medical environments because skilled sleep specialists are needed [6]. Even with known pharmacological and non-pharmacological therapies, approximately 30% of patients continue to experience insomnia.

Non-invasive neurostimulation methods, such as transcranial magnetic stimulation and transcranial direct current stimulation, are largely used as alternative or adjunctive treatments for many neurological and neuropsychiatric disorders. Among them, transcutaneous auricular vagus nerve stimulation (taVNS) has demonstrated a rapid evolution in the past few decades [7]. Transcutaneous electrical stimulation of the concha or the lower half of the back ear (afferent vagus nerve distribution) can produce a similar modulatory effect to that of invasive vagal nerve stimulation (iVNS). In recent years, mounting evidence has supported the therapeutic effects of taVNS for insomnia; however, the potential benefits and clinical role of taVNS in the treatment of insomnia remain uncertain and have not been systematically evaluated. As such, this review aimed to explore the use and effectiveness of alternatives of taVNS in the treatment of insomnia disorder.

SLEEP, STRESS, AND AUTONOMIC NERVOUS SYSTEM DYSFUNCTION

The autonomic nervous system enables the body to maintain homeostasis in response to internal and external stress stimuli by counteracting the sympathetic and parasympathetic nerves. In the transition from the wakeful state to drowsiness and into sleep, parasympathetic vagal tone increases and sympathetic tone decreases. As sleep progresses from light stage 1 non-rapid eye movement (NREM) sleep to the deeper stages (i.e., 2 and 3 NREM sleep), parasympathetic vagal tone increases further. The net result is a reduction in cardiac output, heart rate, and blood pressure [8]. Sympathetic tone continues to decrease at the same time, leading to a reduction in blood pressure and peripheral vascular resistance [8]. For these reasons, NREM sleep can be regarded as a state of parasympathetic dominance, autonomic stability, and metabolic recovery. During REM sleep, cholinergic discharges in the pedunculopontine nucleus and laterodorsal tegmental nucleus of the pons result in muscle atonia that inhibits body movement and dream enactment. REM sleep is divided into tonic and phasic phases. Parasympathetic tone dominates during tonic REM, while the sympathetic tone increases and sympathovagal balance reverses significantly during phasic REM. In this stage of sleep, blood pressure and heart rate may fluctuate dramatically, and blood pressure can reach much higher levels than those in the wakeful state [9]. In this sense, phasic REM can be regarded as a state of heightened sympathetic tone and relative autonomic instability.

Insomnia causes a vicious cycle of stress-insomnia by further activating the hypothalamic-pituitary-adrenal (HPA) system. Stress activates the sympatho-adreno-medullary system and the HPA axis to enhance cardiovascular, as well as catecholamines, cortisol, adrenocorticotropic hormone (ACTH), and corticotrophin-releasing hormone [10]. Chronic stress, in particular, reduces cardiac vagal sensitivity and upregulates the HPA system, resulting in cardiovascular disease and metabolic disturbances. The increase in ACTH levels affects waking time in the morning by changing daily rhythm. Thus, an early rise in sleep after stress may be associated with an early rise in ACTH levels [11]. In chronic stress situations, peripheral corticosteroid levels are elevated and appear to interfere with sleep. Conversely, insomnia also causes a physiological response resembling a stress situation. Sleep has an antagonistic effect on stress by increasing growth hormone and testosterone levels and lowering metabolism and blood flow, while insomnia increases cortisol levels, heart rate, central body temperature, and oxygen consumption [12].

Sleep can be considered a highly complex autonomic function. When sleep is disturbed, many of these homeostatic functions, such as temperature regulation, heart rate variability, and bowel and bladder function, can be affected. Various conditions disrupting the autonomic nervous system also greatly affect sleep.

MECHANISM OF VAGUS NERVE STIMULATION

The 10th cranial nerve (i.e., the vagus nerve) is well known as a parasympathetic nerve that acts as the efferent neurons, but comprises 80% of the afferent sensory nerve fibers that travel toward the brain from various parts of the body including the head, neck, chest, and abdomen. Vagal afferents primarily project to the nucleus tractus solitarius, which in turn projects fibers to various subcortical and cortical structures through the parabrachial nucleus and the locus ceruleus [13]. In particular, the parabrachial nucleus and the locus ceruleus are directly connected to the amygdala and the bed nucleus of the stria terminalis and play an important role in the regulation of emotions. Vagus nerve stimulation (VNS) results in norepinephrine secretion in the solitary nucleus, which promotes stress regulation and secretion of neurotransmitters in the brain by promoting serotonin secretion in the hypothalamus [14]. In addition, the vagus nerve transmits the sensation from the central nervous system to the peripheral sensory canal via the nerve tract. Therefore, VNS has attracted attention as a therapeutic method to indirectly alter brain activity by controlling the far-side sensation [15].

Whether stimulating the vagus nerve, which has sensory afferent connections through the nucleus tractus solitarius, can directly influence diverse brain regions has attracted the attention of many researchers. In 1938, Bailey and Bremer [16] reported that an increased amplitude and frequency of the frontal lobe after direct stimulation of the vagus nerves in cats. In 1951, Dell and Olson [17] reported that the stimulation of the vagus nerves affected the rhinal sulcus and amygdala in awake cats. Zabara et al. [18] reported that stimulation of the vagus nerves had an inhibitory effect on emesis via restraining the contractions of the abdomen. This was followed by a study in which repetitive VNS demonstrated anticonvulsant action. It was hypothesized that VNS could prevent or control the motor and autonomic components of epilepsy [19]. Eventually, VNS become approved as a treatment for epilepsy.

VNS FOR THE TREATMENT OF PSYCHIATRIC DISORDERS

In addition to epilepsy, research investigating the therapeutic effect of VNS in patients with depression has been actively conducted. In an animal study, Furmaga et al. [20] found that repeated administration of VNS decreased the latency to feed in the novelty-suppressed feeding test and immobility in the forced swim test, which is consistent with the antidepressant-like effects of VNS. In particular, lesioning either serotonergic or noradrenergic systems completely abolished VNS-induced antidepressant effects. Another study reported that VNS increased the firing activity and pattern of norepinephrine and 5-hydroxytryptamine neurons [14]. These studies provide the evidence that VNS directly stimulates the activity of serotonin and norepinephrine neurons.

In 2005, the United States Food and Drug Administration (FDA) approved the use of VNS for the adjunctive long-term treatment of treatment-resistant depression (TRD). First, a short-term VNS add-on study showed that 40% of TRD patients were considered to be responders based on Hamilton Depression Rating Scale (HDRS) scores, while 17% were in remission [21]. A subsequent study also demonstrated that VNS significantly improved depressive symptoms after 10 weeks of treatment [22]. Four of 7 patients exhibited a 50% reduction in the HDRS-28, and 2 of these remitted. In a one-year, naturalistic, prospective study, George et al. [23] compared two non-randomized groups of patients with refractory depression, and reported greater efficacy for the group that received VNS along with treatment as usual compared with the group that only received treatment as usual. The only double-blind randomized study revealed that the mean HDRS-24 response rates of both active VNS and sham groups improved to comparable levels, indicating that there is no significant difference between the groups. However, in a secondary outcome (the Inventory of Depressive Symptomatology), a significant difference was found [24]. Results of a recent meta-analysis investigating efficacy in uncontrolled studies revealed a significant reduction in scores at the HDRS endpoint [25]. The percentage of responders was 31.8%. VNS appears to be a good alternative long-term treatment, especially for TRD.

VNS AND SLEEP

Previous research has demonstrated the effect of VNS on sleep. One polysomnographic study involving patients with refractory epilepsy demonstrated a significant reduction in REM sleep and an enhancement of delta power during NREM sleep after chronic administration of VNS [26]. Subjective data derived from the sleep-wake diary revealed a significant decrease in daytime naps and daytime sleepiness, and an increase in daytime alertness. These effects were interpreted to be the result of a destabilizing action of VNS on neural structures regulating sleep-wake and REM-NREM sleep cycles. Another study evaluated the effects of VNS on sleep in patients with TRD [22]. Decreased awake time, decreased stage 1 sleep and increased stage 2 sleep were evident 10−12 weeks after VNS implantation, and significant reductions in depressive symptom severity was observed. In addition, the amplitude of electroencephalographic ultradian sleep rhythms was significantly increased. These results suggest that VNS treatment could improve both the clinical symptoms of depression and sleep architecture. Overall, VNS has an effect on the sleep-wake cycle and sleep microarchitecture and, therefore, can positively help individuals with insomnia.

CLINICAL IMPLICATIONS OF taVNS

VNS was approved by the FDA for epilepsy in 1997 and for TRD in 2005. However, some factors have limited the use of VNS, including high cost, requirement for surgery, and potentially significant side effects such as postoperative infection, hoarseness, and bradycardia [27]. Transcutaneous electrical stimulation of the auricular concha can produce a similar modulatory effect to that of iVNS and has several advantages; in particular, it does not require surgical intervention for electrode implantation. In recent years, several clinical trials have explored the therapeutic effects of taVNS for managing major depressive disorder (MDD). The first clinical trial of taVNS for MDD revealed that the taVNS group exhibited significant improvement on the Beck Depression Inventory after a 2-week treatment compared with the sham-treated group [28]. However, there was no significant difference in the HDRS scores between the two groups. Rong et al. [29] investigated the effect of taVNS treatment by training patients to apply bilateral taVNS at home. After four weeks, the taVNS group exhibited greater decreases in the 24-item Hamilton Rating Scale for Depression (HAMD) score and higher rates of good responders than those in the sham taVNS group. The clinical improvements continued until week 12. A recent single-arm study reported that 17-item HAMD scores were significantly reduced after 2-weeks of taVNS treatment [30]. All patients exhibited a clinical response, defined as a reduction in HAMD scores of at least 50%, and the effect persisted 1 month after treatment.

POTENTIAL OF taVNS IN THE TREATMENT OF INSOMNIA

A recent case report demonstrated improvement in insomnia symptoms after four weeks of taVNS treatment [31]. Sleep duration was increased up to 7 h, and sleep onset time was reduced to <30 min. The Pittsburgh Sleep Quality Index score decreased from 13 to 8. The functional connectivity between the posterior cingulate cortex and other brain regions belonging to the default mode network (DMN) showed higher functional connectivity before treatment, and DMN connectivity decreased after four weeks of taVNS treatment. DMN functional connectivity in insomnia has been associated with hyperarousal symptoms.

In addition to effectiveness, taVNS is known to be a safe and highly tolerable method, given that most previously reported side effects have been mild. They include tinnitus or acceleration of original tinnitus, and local problems at stimulation sites, such as pain, paresthesia, or pruritus during or after stimulation [32]. Because there are no direct fibers connecting the auricular branch of the vagus nerve to the heart, both left and right ears should be safe for applying taVNS [33]. A recent study reported that taVNS has no arrhythmic effects on cardiac function in tinnitus patients with no known pre-existing cardiac pathology [34].

CONCLUSION

Noninvasive brain stimulation has recently received much attention in the field of neuroscience. Various brain stimulation methods have become noteworthy therapeutic alternatives to treat various mental disorders. In particular, it is easy to obtain

patients' consent for taVNS treatment, and there is a possibility of rapid clinical application in the future due to the low number of side effects. Therefore, taVNS remains a potential alternative treatment for individuals with insomnia because prolonged drug intake could result in serious side effects, the development of tolerance, dependence, and the rebound effect. Non-pharmacological approaches, such as cognitive-behavioral therapy, have also shown limited effectiveness. Therefore, future studies investigating the applicability of taVNS could provide a variety of treatment options for insomnia, as well as better understanding of the pathophysiology of the insomnia.

Conflicts of Interest

The author has no potential conflicts of interest to disclose.

ORCID iD

Ho-Kyoung Yoon
https://orcid.org/0000-0002-3302-0660

REFERENCES

1. Zammit GK, Weiner J, Damato N, Sillup GP, McMillan CA. Quality of life in people with insomnia. Sleep 1999;22 Suppl 2:S379-S385.
2. Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. J Clin Sleep Med 2008;4:487-504.
3. Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? JAMA 1989;262:1479-1484.
4. Chang CM, Wu EC, Chen CY, Wu KY, Liang HY, Chau YL, et al. Psychotropic drugs and risk of motor vehicle accidents: a population-based case-control study. Br J Clin Pharmacol 2013;75:1125-1133.
5. Gray SL, LaCroix AZ, Hanlon JT, Penninx BW, Blough DK, Leveille SG, et al. Benzodiazepine use and physical disability in community-dwelling older adults. J Am Geriatr Soc 2006;54:224-230.
6. Morin CM. Cognitive-behavioral approaches to the treatment of insomnia. J Clin Psychiatry 2004;65 Suppl 16:33-40.
7. Capone F, Assenza G, Di Pino G, Musumeci G, Ranieri F, Florio L, et al. The effect of transcutaneous vagus nerve stimulation on cortical excitability. J Neural Transm (Vienna) 2015;122:679-685.
8. Van de Borne P, Nguyen H, Biston P, Linkowski P, Degaute JP. Effects of wake and sleep stages on the 24-h autonomic control of blood pressure and heart rate in recumbent men. Am J Physiol 1994;266(2 Pt 2):H548-H554.
9. Somers VK, Dyken ME, Mark AL, Abboud FM. Sympathetic-nerve activity during sleep in normal subjects. N Engl J Med 1993;328:303-307.
10. Cacioppo JT, Berntson GG, Malarkey WB, Kiecolt-Glaser JK, Sheridan JF, Poehlmann KM, et al. Autonomic, neuroendocrine, and immune responses to psychological stress: the reactivity hypothesis. Ann N Y Acad Sci 1998;840:664-673.
11. Born J, Hansen K, Marshall L, Mölle M, Fehm HL. Timing the end of nocturnal sleep. Nature 1999;397:29-30.
12. Bonnet MH, Arand DL. 24-Hour metabolic rate in insomniacs and matched normal sleepers. Sleep 1995;18:581-588.
13. Ricardo JA, Koh ET. Anatomical evidence of direct projections from the nucleus of the solitary tract to the hypothalamus, amygdala, and other forebrain structures in the rat. Brain Res 1978;153:1-26.
14. Manta S, Dong J, Debonnel G, Blier P. Enhancement of the function of rat serotonin and norepinephrine neurons by sustained vagus nerve stimulation. J Psychiatry Neurosci 2009;34:272-280.
15. Frangos E, Ellrich J, Komisaruk BR. Non-invasive access to the vagus nerve central projections via electrical stimulation of the external ear: fMRI evidence in humans. Brain Stimul 2015;8:624-636.
16. Bailey P, Bremer F. A sensory cortical representation of the vagus nerve (with a note on the effects of low blood pressure on the cortical electrograms). J Neurophysiol 1938;1:405-412.
17. Dell P, Olson R. [Thalamic, cortical and cerebellar projections of vagal visceral afferences]. C R Seances Soc Biol Fil 1951;145:1084-1088.
18. Zabara J, Chaffee RB Jr, Tansy MF. Neuroinhibition in the regulation of emesis. Space Life Sci 1972;3:282-292.
19. Zabara J. Peripheral control of hypersynchronous discharge in epilepsy. Electroencephalogr Clin Neurophysiol 1985;61(Suppl):S162.
20. Furmaga H, Shah A, Frazer A. Serotonergic and noradrenergic pathways are required for the anxiolytic-like and antidepressant-like behavioral effects of repeated vagal nerve stimulation in rats. Biol Psychiatry 2011;70:937-945.
21. Rush AJ, George MS, Sackeim HA, Marangell LB, Husain MM, Giller C, et al. Vagus nerve stimulation (VNS) for treatment-resistant depressions: a multicenter study. Biol Psychiatry 2000;47:276-286.
22. Armitage R, Husain M, Hoffmann R, Rush AJ. The effects of vagus nerve stimulation on sleep EEG in depression: a preliminary report. J Psychosom Res 2003;54:475-482.
23. George MS, Rush AJ, Marangell LB, Sackeim HA, Brannan SK, Davis SM, et al. A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. Biol Psychiatry 2005;58:364-373.
24. Rush AJ, Marangell LB, Sackeim HA, George MS, Brannan SK, Davis SM, et al. Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. Biol Psychiatry 2005;58:347-354.
25. Martin JL, Martín-Sánchez E. Systematic review and meta-analysis of vagus nerve stimulation in the treatment of depression: variable results based on study designs. Eur Psychiatry 2012;27:147-155.
26. Rizzo P, Beelke M, De Carli F, Canovaro P, Nobili L, Robert A, et al. Chronic vagus nerve stimulation improves alertness and reduces rapid eye movement sleep in patients affected by refractory epilepsy. Sleep 2003;26:607-611.
27. Daban C, Martinez-Aran A, Cruz N, Vieta E. Safety and efficacy of Vagus Nerve Stimulation in treatment-resistant depression. A systematic review. J Affect Disord 2008;110:1-15.
28. Hein E, Nowak M, Kiess O, Biermann T, Bayerlein K, Kornhuber J, et al. Auricular transcutaneous electrical nerve stimulation in depressed patients: a randomized controlled pilot study. J Neural Transm (Vienna) 2013;120:821-827.
29. Rong P, Liu J, Wang L, Liu R, Fang J, Zhao J, et al. Effect of transcutaneous auricular vagus nerve stimulation on major depressive disorder: a nonrandomized controlled pilot study. J Affect Disord 2016;195:172-179.
30. Trevizol AP, Taiar I, Barros MD, Liquidatto B, Cordeiro Q, Shiozawa P. Transcutaneous vagus nerve stimulation (tVNS) protocol for the treatment of major depressive disorder: a case study assessing the auricular branch of the vagus nerve. Epilepsy Behav 2015;53:166-167.
31. Zhao B, Li L, Jiao Y, Luo M, Xu K, Hong Y, et al. Transcutaneous auricular vagus nerve stimulation in treating post-stroke insomnia monitored by resting-state fMRI: the first case report. Brain Stimul 2019;12:824-826.
32. Straube A, Ellrich J, Eren O, Blum B, Ruscheweyh R. Treatment of chronic migraine with transcutaneous stimulation of the auricular branch of the vagal nerve (auricular t-VNS): a randomized, monocentric clinical trial. J Headache Pain 2015;16:543.
33. Sperling W, Reulbach U, Bleich S, Padberg F, Kornhuber J, Mueck-Weymann M. Cardiac effects of vagus nerve stimulation in patients with major depression. Pharmacopsychiatry 2010;43:7-11.
34. Kreuzer PM, Landgrebe M, Husser O, Resch M, Schecklmann M, Geisreiter F, et al. Transcutaneous vagus nerve stimulation: retrospective assessment of cardiac safety in a pilot study. Front Psychiatry 2012;3:70.