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Effect of Vagus Nerve Stimulation on Subjective Tinnitus

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Abstract

Background: **subjective tinnitus is a phantom sensation experienced in the absence of any internal or external acoustic stimulus. At present, tinnitus has become the most common Otologic problem, affecting 15% to 20% of the general population.** ***Objective:*** **To determine if vagus nerve stimulation can improve quality of life in patients with sensorineural hearing loss (SNHL) suffering from subjective tinnitus.** ***Patients and Methods:*** **This prospective quasi-experimental study was carried out on 29 patients presented to the Audiovestibular Medicine outpatient clinic in SCU hospital during the period from July 2019 to January 2020. patients complaining from non-pulsatile continuous subjective tinnitus and diagnosed with mild to moderate SNHL were included. The full audiological evaluation was done in addition to transcutaneous electrical nerve stimulation (7 sessions) and the severity of tinnitus was assessed before and after TENS stimulation by using the Arabic translation of the Tinnitus Handicap Inventory(THI) questionnaire.** ***Results±:*** **Transcutaneous vagus nerve stimulation had elicited a statistically significant decrease in THI score (p<0.001). females had significantly higher THI scores compared to males before nerve stimulation (p=0.008). Moreover, females were found to have significantly higher THI scores compared to males after nerve stimulation (p=0.037).** ***Conclusion:*** **1- Transcutaneous Vagus nerve stimulation (t-VNS) was effective in reducing THI score denoting reduced handicap in patients with SNHL complaining of tinnitus. 2- Neither participants' characteristics nor disease characteristics were associated with a better outcome. 3- Irrespective of age or tinnitus duration, t-VNS could improve tinnitus complaint.**

Keywords: tinnitus, sensorineural hearing loss, vagus nerve, transcutaneous electrical nerve stimulation

Introduction

Subjective tinnitus is considered a phantom sensation experienced in the absence of any internal or external acoustic stimulus. It can be perceived as a hissing, buzzing, roaring, whistling, or ringing sound in one or both ears[(1)]. At present, tinnitus has become the most common otologic problem, affecting 15% to 20% of the general population. Among severe tinnitus sufferers, tinnitus-related sensations, such as anxiety, annoyance, frustration, and depression lead to a negative impact on quality of life in 70% of those affected[(2)]. The possible etiologies that may lead to tinnitus include auditory alteration-related conditions such as presbycusis, noise-induced hearing loss, and sudden

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hearing loss. Somatosensory-auditory interactions such as a patulous eustachian tube, myoclonus, and spasm of stapedius muscle or tensor tympani. Psychiatric disorders such as depression, anxiety, or obsessive-compulsive disorder[3]. The pathological mechanisms that underlie tinnitus perception remain largely hypothetical and are still not well understood. Currently, the universally accepted hypothesis is that interactions between altered cochlear inputs and distorted central auditory processing provoke tinnitus[4,5]. The vagus nerve is the longest cranial nerve and is involved in the control of various functions of the entire body, including parasympathetic innervations to the heart, lung, and digestive organs; branchial motor functions, such as swallowing and speaking; and somatic and visceral sensations[6]. Neuro-modulation is a physiological process that consists of the alteration of neuronal and synaptic properties by neurons or substances released by neurons[7]. Neuro-stimulation impacts the release of neurotransmitters and thus on the activity of the central nervous system (CNS). By changing neurotransmitters' concentration in specific brain regions, neuro-modulation may modify the intrinsic properties of neuron membrane thus altering response to synaptic events[8]. In invasive vagus nerve stimulation, an electrode surgically implanted around the left cervical vagus nerve is connected to a pulse generator placed subcutaneously in the upper chest. However, considering the disadvantages of the implantation, a relatively safe and well-tolerated improved method is desired. To minimize side effects, stimulation of the auricular branch of the vagus nerve (ABVN) has been suggested[9]. Treatment for tinnitus includes correcting identified comorbidities as well as directly addressing the effects of tinnitus on quality of life. Several treatment modalities have been studied, and no treatment domain can be identified as holding a prime position in the therapeutic spectrum[10] Our present study aimed to determine if transcutaneous vagus nerve stimulation can improve the quality of life in patients with mild to moderate sensorineural hearing loss suffering from subjective tinnitus.

Subjects and Methods

Subjects

This study was conducted after medical ethics committee approval, in the audio-vestibular unit of the ENT department. Suez Canal University Hospital. 29 patients, aged from 35 to 75 years, with acute or chronic non pulsatile continuous tinnitus, not using hearing aids, and diagnosed with mild to moderate sensorineural hearing loss (SNHL) were included in our study. Exclusion criteria included pregnancy, patients with pulsatile tinnitus, or under medical treatment for tinnitus. Patients with conductive or mixed hearing loss or other degrees (severe or profound) of sensorineural hearing loss, patients with cardiac disease, wounds or diseased skin, metal pieces in the body (pacemaker), active implants such as a cochlear implant, or the presence of an implantable metal device in the cranial region, also were excluded.

Methods

This study was a prospective quasi-experimental study (pre and post-intervention study)

All subjects in this study were treated similarly and they were subjected to:

1- *History taking:* to obtain Personal data, complaint analysis, otologic symptoms, history of chronic diseases, family history, and drug history.
2- *Questionnaire:* The Arabic translation of the Tinnitus Handicap Inventory (THI) questionnaire[11,12]was used for assessment of the severity of tinnitus before and after TENS stimulation.

3- *General Medical evaluation:* To check on the inclusion and exclusion criteria

4- *Otoscopic examination*: To Inspect the external auditory canal and to evaluate the tympanic membrane

5- *Basic Audiological Assessment, including* a) Pure tone audiometry for octave frequencies 250-8000 Hz for air conduction and 500-4000Hz for bone conduction, using pulsed stimulus. b) Speech Audiometry including i) speech reception threshold (SRT), using Arabic spondaic words[13] and, ii) word discrimination score (WDS), using Arabic phonetically balanced words[14]. c) Tympanometry and acoustic reflex threshold measurement with a probe tone of 226 Hz and for the ipsilateral and contralateral elicited reflexes, using pure tones at frequencies 500, 1000, 2000, and 4000 Hz.

6- *Transelectrical nerve stimulation:* (7 sessions each lasting 45-60 min)[15]. The stimulation conditions were as follows: Pulse width 250 µs, frequency 25 Hz, stimulation site was cymba concha and intensity increased by 1 mA every 5 s until the maximum intensity that the patients could tolerate without feeling pain[16]. To minimize cardiac side effects, only the left vagus nerve was stimulated, and all patients were monitored for heart rate during the first session. The rationale for stimulating the left vagus nerve is that it innervates the atrioventricular (AV) node, so it is more associated with the ventricles of the heart controlling the contraction forces. On the other hand, the right vagus nerve is more closely associated

7- with the cardiac atria as it innervates the sinoatrial (SA) node controlling the heart rate. Stimulation of each vagus nerve produces effects on the heart consistent with such innervation[17,18].

Results

The mean age of the patients was 58.34 ± 10.55 years and about half of the patients were males (51.7%). Illiterate or patients who could read and write only formed 20.7% of the sample. About 80% of the patients are not working and almost half of the sample had moderate high-frequency audiometric configuration (44.8%) as shown in table 1. Table 2 shows that transcutaneous vagus nerve stimulation had elicited a statistically significant decrease in the tinnitus handicap inventory (THI) score (44.97 ± 21.37 vs 32.28 ± 2.12) ($p<0.001$). Table 3 shows that there is no statistically significant association between change in tinnitus handicap inventory (ΔTHI) score before and after nerve stimulation and baseline characteristics of participants. Table 4 shows that participants with long-term clinical improvement showed more reduction in (Δ THI) score than those who did not (-24.67± 4.5 *vs.* -9.57±8.33) ($p=0.001$). Table 5 shows that females had significantly higher THI scores compared to males before nerve stimulation (55.57 ± 19.02 vs 35.07 ± 18.95) ($p=0.008$). Moreover, females were found to have significantly higher THI scores compared to males after nerve stimulation (40.29 ± 19.99 vs 24.8 ± 15.35) ($p=0.037$). Multivariable linear regression analysis was used to assess predictors of THI scores after nerve stimulation among patients complaining of tinnitus. R2 =0.79.2, where 79.2% of the variability among patients complaining of tinnitus can be explained by this linear model. It was found that for every one-point increase in the THI scores before stimulation, there is an increase in the THI scores after stimulation by 0.78 points (β= 0.783, p<0.001). In other words, patients with a lower pre-intervention score were found to have a better outcome (more reduction in THI score) when compared to those patients with a higher pre-intervention score (Table 6). No statistically significant correlation was found between the age of the patients or duration of symptoms and change in THI score (Table 7).

Discussion

This study explored the effect of transcutaneous Vagus nerve stimulation (t-VNS) in patients with SNHL complaining of tinnitus and was carried out in the audiovestibular clinic- Suez Canal University Hospital.

Table 1. Baseline Characteristics of the Patients

Variables	n= 29
Age, years	
mean ± SD	58.34 ± 10.55
median (range)	62 (35 – 72)
Gender, n (%)	
Male	15 (51.7)
Female	14 (48.3)
Education level, n (%)	
Illiterate/ Read and write	6 (20.7)
Low educational level	4 (13.8)
Moderate educational level	10 (34.5)
High educational level	9 (31)
Occupation, n (%)	
Not working	23 (79.3)
Working	6 (20.7)
Audiometric configuration, n (%)	
High frequency (mild)	7 (24.1)
High frequency (moderate)	13 (44.8)
Flat (mild)	4 (13.8)
Flat (mild to moderate)	2 (6.9)
Flat (moderate)	3 (10.3)

Data are presented as numbers (%) or mean and SD.

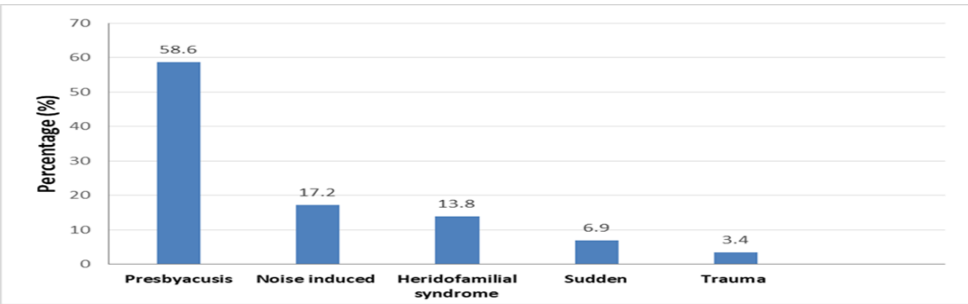

Figure 1. Distribution of causes of tinnitus among the study participants

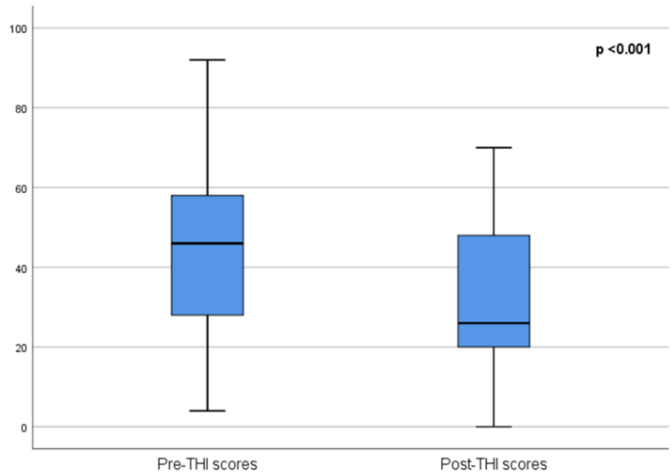

Figure 2. Comparison between tinnitus handicap inventory (THI) scores before and after transcutaneous vagus nerve stimulation

Table 2. Comparison of tinnitus handicap inventory (THI) scores before and after transcutaneous vagus nerve stimulation

Variables	Pre-intervention (n=29)	Post-intervention (n=29)	p-value*
THI scores	44.97 ± 21.37	32.28 ± 2.12	<0.001 a

**Wilcoxon signed-rank test. Statistical significance at P < 0.05*
Data are presented as mean ± SD

All patients in the study were not using hearing aids and to facilitate communication, only patients with mild to moderate degree of hearing loss were included. All patients were treated similarly as they were subjected to transcutaneous vagus nerve stimulation using TENS 7000 device (Seven sessions, each lasting 45–60 min and delivered for 10 days). The study included 29 patients who matched our inclusion criteria, the mean age of patients was 58.34 years. Fifteen patients were males, and fourteen patients were females. Illiterate or patients who could read and write only formed 20.7% of the sample and since it was known that participants with a low educational level have lower self-esteem, cognitive and control capacities compared with those with a higher educational level[19], then the level of education was important to be considered when studying the association between characteristics of participants and degree of improvement or change in THI score after t-VNS. The results in the current study also showed that 80% of the patients were not working and it was found that patients having less work remain longer in their homes where silence and auditory attention could be more relevant for increasing the perception of annoyance due to tinnitus. This could be the reason why nonworkers were more prone to seek medical help which was reflected by the high percentage of non-workers in the study. In the current study, as shown in figure 1, more than half of the causes of tinnitus were due to presbyacusis (58.6%). The epidemiological data had generally supported a strong association of tinnitus with increasing age; in particular, the decade of age which was more frequently affected was between 61 and 70 followed by lower decades[20–22]. It was probably due to the degree of hearing impairment and to the high incidence of predisposing conditions (cardiovascular and metabolic diseases). Benevides[23] also reported that tinnitus often accompanies presbyacusis and maybe even more troublesome than deafness. Our results showed that 68.9% of the patients had high frequency (mild & moderate) audiometric configuration.

Table 3: Relationship of baseline characteristics of participants with ΔTHI scores

Variables	ΔTHI scores	p-value
Gender		
Male	-10.27 ± 8.71	0.25[a]
Female	-15.29 ± 10.63	
Education level		
Illiterate/ Read and write	-11.67 ± 10.07	0.9[b]
Low educational level	-14.50 ± 16.92	
Moderate educational level	-12.2 ± 8.97	
High educational level	-13.11 ± 8.67	
Occupation		
Not working	-12.35 ± 9.51	0.62[a]
Audiometric configuration		
High frequency (mild)	-8.86 ± 9.44	0.78[b]
High frequency (moderate)	-13.69 ± 10.61	
Mild (flat)	-14 ± 10.46	
Mild to moderate	-14± 14.14	
Moderate	-14.67 ± 9.02	

[a]*Mann Whitney U test.* [b]*Kruskal Wallis test.*
Data are presented as mean ± SD, *Statistical significance at P <0.05*

This agreed with the results of a study investigating tinnitus patients in Italy which showed that 72.10% of the patients had high-frequency audiometric configuration[24]. This could be correlated to the high percentage of patients having tinnitus due to presbyacusis in which hearing loss is known to be most marked at higher frequencies. In the current study, assessment of the outcome was subjective using Tinnitus Handicap Inventory (THI) questionnaire and the results showed that there was a statistically significant decrease in THI score after transcutaneous electrical vagus nerve stimulation indicating reduced handicap. On the contrary, Kreuzer PM, et al[25] claimed that no clinically relevant improvement of tinnitus complaints was observed after transcutaneous VNS. This discrepancy might be due to differences in the assessment tools as their study was conducted in two phases applying two different stimulating devices (CM02 in phase 1 and NEMOS in phase 2). Brain scans through fMRI had implicated specific brain regions to be involved in the perception and generation of tinnitus. These regions were the parahippocampal gyrus, the amygdala, and the hippocampus (limbic areas of the brain). The vagus nerve passes via the outer ear to the nucleus of the solitary tract (NTS) and on to these brain regions. Vagus nerve stimulation can target these specific areas of the brain to reduce overactivity and break the cycle of the limbic distress network[26,27]. It does so through the action of several neuromodulators including the modulation of norepinephrine release via projections extending from NTS to the locus coeruleus, which subsequently influence the limbic, reticular, and autonomic centers of the brain. This was done using a small handheld neurostimulation device and electrode clipped to the outer ear, so it was possible to target and directly modulate the brain *via* the vagus nerve[28]. In this study, there was no significant association between the characteristics of participants (i.e., gender, educational level, occupation, or audiometric configuration) and change in tinnitus handicap inventory (ΔTHI) score.

Table 4: Relationship of disease characteristics of participants with Δ THI scores

Variables	Δ THI scores	p-value
Affected side (complaint)		
Unilateral	-11.78 ± 8.97	0.73[a]
Bilateral	-13.1 ± 10.41	
Etiology		
Presbyacusis	-12.5 ± 10.52	0.36[b]
Sudden	-21. ± 4.24	
Heridofamilial syndrome	-14.5 ± 12.26	
Noise-induced	-6 ± 2.83	
Trauma	-12 ± 1.9	
Cervical	-26 ± 14.6	
History of previous medical treatment		
No treatment	-8.75 ± 8.29	0.09[b]
Treatment ginkgo	-16.91 ± 10.41	
Treatment sudden	-21 ± 4.24	
Long term improvement		
Not improved	-9.57 ± 8.33	0.001[a]
Improved	-24.67 ± 4.5	

[a]Mann Whitney U test. [b]Kruskal Wallis test.
Statistical significance at p <0.05, Data are presented as mean ± SD

Negrila-Mezei, et al. studied tinnitus in the elderly population and reported that variables like gender, residence, and economic status were not significantly associated with tinnitus[29]. Moreover, the results of Shargorodsky, et al.[30] agreed with the results of the current study concerning the level of education. It was known that the frontal lobe is the area of the brain involved in reasoning as it contains the prefrontal cortex which is responsible for higher-level cognitive functioning and since this brain region is not involved in the mechanism of reducing tinnitus via vagus nerve stimulation as mentioned above, we cannot speculate an association between level of education and degree of improvement in tinnitus. The different patient responses and the variable degrees of improvement with vagus nerve stimulation might be due to anatomical variations in the connections along the pathway of stimulation as it was noted that participants had different sensitivity to the intensity of stimulation with the TENS device. The current study also showed that the disease characteristics of the participants (including affected side or etiology) had no association with change in tinnitus handicap inventory (ΔTHI) score. The results of a case series study in which VNS was paired with tones, did not indicate that specific patient had a better response due to spe cific tinnitus characteristics (including the etiology of tinnitus- tinnitus laterality- the tinnitus frequency of tinnitus pitch) which was consistent with the results of the current study[31].

Table 5: Relationship of baseline characteristics of participants with THI scores				
Variables	pre-THI scores mean ± SD	p-value	post-THI scores mean ± SD	p-value
Gender				
Male	35.07 ± 18.95	0.008[a]	24.8 ± 15.35	0.037[a]
Female	55.57 ± 19.02		40.29 ± 19.99	
Education level				
Illiterate/ Read and write	47 ± 16.33	0.93[b]	35.33 ± 24.71	0.93[b]
Low educational level	49 ± 26.20		34.5 ± 16.11	
Moderate educational level	45.8 ± 25.44		33. ± 21.2	
High educational level	40.89 ± 20.35		27.78 ± 16.13	
Occupation				
Not working	42.96 ± 21.3	0.36[a]	30.61 ± 19.7	0.23[a]
Working	52.67 ± 21.56		38.67 ± 16.4	
Audiometric configuration				
High frequency (mild)	45.71 ± 18.27	0.78[b]	36.86 ± 18.5	0.66[b]
High frequency (moderate)	50 ± 24.42		36.31 ± 20.8	
Mild (flat)	35 ± 10.89		21 ± 11.6	
Mild to moderate	37 ± 46.7		23± 32.52	
Moderate	40 ± 8.71		25.33 ± 12.85	

a=Mann Whitney U test. b=Kruskal Wallis test. Statistical significance at p <0.05

Table 6: Multivariable linear regression analysis of determinants of THI scores after intervention					
Predictors	Unstandardized Coefficients		Standardized Coefficients	95% CI	P-value
	B	Std. Error	Beta		
(Constant)	5.210	12.747			0.686
Preintervention THI score	0.783	0.100	0.875	(0.578 – 0.989)	<0.001*
Age	-0.118	0.178	-0.065	(-0.484 – 0.248)	0.512
Female *vs.* Male (R)	-0.852	3.941	-0.023	-(8.969 – 7.266)	0.831

*ANOVA < 0.001, R2= 79.2%, * Statistical significance at p < 0.05*

On the other side, previous research on transcranial magnetic sitmulation[32,33], and transcranial direct current stimulation[34] indicated that the outcome could depend on specific tinnitus characteristics. There was no agreement on how to measure tinnitus loudness and the precise methodology was often under-reported. Descriptions for loudness matching included matching at 1 kHz, psychoacoustic measure, and by audiometry[35]. The use of psychoacoustic measures such as the Minimum Masking Level (MML) had been problematic in earlier studies[36] and loudness matching was known to be subject to learning effects[37]. So, we did not consider tinnitus frequency of tinnitus pitch when studying the disease characteristics. In the current study, participants with more reduction in (Δ THI) score were found to have more long-term clinical improvement as shown in table 4. Few studies of the efficacy of tinnitus treatments had assessed their long-term effects on tinnitus severity.

Table 7: Correlation between Δ THI score and different clinical variables		
Variables	Δ THI scores	
	r	p-value
Age	0.078	0.688
Duration of symptoms	-0.034	0.862

[a]= *Spearman's correlation coefficient. Statistical significance at p <0.05*

This was an important point to consider because patients' perception of their tinnitus often changes with time. Scott, et al.[38] had published the effects of a relaxation/distraction counseling program four weeks after treatment and found that the patients improved significantly in discomfort and irritation from tinnitus as well as in depression and reported loudness of tinnitus. On the other hand, Lindberg et al.[39] assessed tinnitus severity on the same patients, nine months after they had completed the same treatment program and found that significant improvement remained for discomfort from tinnitus only while responses to the other severity measures were no longer significantly different from pre-treatment values. In the current study, it was found that females had significantly higher THI scores compared to males before nerve stimulation. This coincides with the results of Seydel et al[40] which showed that irrespective of age and tinnitus duration, women were more annoyed by tinnitus and perceived more stress than men did and the scores of tinnitus annoyance were significantly higher in women than in men. Their study also showed that women scored lower than men in proactive coping, sense of coherence, and personal resources. Females have a completely different hormonal system which causes them to react more emotionally and become more exhausted on an emotional level. Furthermore, females are exposed to more stress factors as they must assume many roles in their day to day and since the neurophysiological model devised by Jastreboff suggested that tinnitus is linked with auditory perceptual, emotional, and reactive systems, then the negative emotional reinforcement by the limbic system and autonomic activation may enhance tinnitus perception in females making a positive feedback loop. Moreover, in the current study, females were found to have significantly higher THI scores compared to males after nerve stimulation. This could be demonstrated by a multivariable linear regression analysis in which it was found that for every one-point increase in the THI scores before stimulation, there was an increase in the THI scores after stimulation by 0.78 points. In other words, for every 10 points increase in the pre-THI score, there was an increase in the post-THI score by 7.8 points. Neuroplasticity is the capacity of the brain to reorganize and adapt in response to internal or external stimulation. It has been assumed that brain plasticity peaks at a young age and then gradually decreases as one gets older[41]. Some studies investigating the effect of vagus nerve stimulation in the treatment of epilepsy showed that the age of implantation of VNS device <18 years was associated with better response[42]. On the contrary, our study showed no correlation between the age of patients and the degree of improvement or change in THI score. Normal aging is associated with changes in autonomic nervous system (ANS) function and is characterized by increases in sympathetic and decreases in parasympathetic nervous activity[43]. A study investigating the effects of t-VNS in individuals aged 55 years or above showed that t-VNS could induce a shift in ANS function from sympathetic preponderance towards parasympathetic predominance. Moreover, it was found that t-VNS for only 15 minutes per day for 14 days decreased the need for vasodilator medication and improved exercise tolerance in patients with coronary artery disease. Furthermore, tVNS reduced atrial fibrillation in patients with paroxysmal atrial fibrillation (PAF). It also showed that the high initial sympathetic prevalence was associated with greater improvements[44]. Since the main problem of patients with disturbing tinnitus is tinnitus-related mental stress which is associated with an imbalance of the ANS with sympathetic preponderance and corresponding reduced parasympathetic activity and since older patients have high initial sympathetic prevalence which was associated with greater improvements in the previous studies. Then, this could explain the absence of the correlation between the age of patients and the degree of improvement in the current study as younger patients have more neuroplasticity while older patients have high initial sympathetic prevalence. Finally, transcutaneous vagus nerve stimulation by TENS device can be adopted, in a wide range of patients, as a new therapeutic approach in the treatment of subjective tinnitus with mild to moderate SNHL especially it was found to be safe, with negligible side effects, its application is easy, and it is not expensive.

Conclusions

Transcutaneous Vagus nerve stimulation (t-VNS) was effective in reducing THI score denoting reduced handicap in patients with mild to moderate SNHL complaining of tinnitus. Neither participants' characteristics nor disease characteristics were associated with a better outcome. This study also showed that irrespective of the patient's age or tinnitus duration, t-VNS could improve tinnitus complaints.

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