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Tinnitus perception in patients after vagal nerve stimulator implantation for epilepsy

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A B S T R A C T

Purpose: Vagal nerve stimulation in conjunction with sound therapy has been proposed as a treatment for subjective tinnitus. The purpose of this study is to retrospectively review the effect of VNS on perception of tinnitus in epilepsy patients. We explore the incidence of tinnitus and its perceived reduction in patients requiring implantation of VNS for medically refractory seizures.

Materials and methods: A phone survey was conducted in adult patients with prior VNS implantation. A questionnaire including the visual analog scale (VAS) of tinnitus loudness was used to determine the presence and severity of tinnitus.

Results: Out of the 56 patients who had completed the phone survey, 20 (35%) reported the presence of pre-operative tinnitus. The tinnitus positive group was significantly older ($p = 0.019$). Of the 20 pre-operative tinnitus positive patients, all patients continued to have tinnitus post-operatively. Four (20%) noted no changes in VAS of tinnitus loudness while 16 (80%) had at least a one-point decrease. The mean difference between pre- and post-operative VAS of loudness was 2.05, with a standard deviation of 1.84 and this was statistically significant ($p < 0.001$).

Conclusions: In this study, we evaluate the potential of vagal nerve stimulation to alter the perception of tinnitus in patients with refractory epilepsy. Eighty percent of patients noted some level of subjective tinnitus improvement after VNS implantation. Given this finding, there may be a potential additional benefit to the use of VNS in patients with epilepsy.

1. Introduction

Tinnitus is a common condition affecting approximately 10–20% of the US population [1]. More than 99% of tinnitus is in the form of subjective patient complaints [1]. Tinnitus treatment options are as diverse as their efficacy. Both pharmacologic and non-pharmacologic modalities have been used with only limited success [2]. The etiology of tinnitus is controversial, with one of the main theories suggesting that cochlear damage produces changes in tonotopy resulting in hyperactivity of the auditory cortex [3]. Cortical reorganization results in the perception of sound when no sound is present; this is perceived as subjective tinnitus [4]. Given these findings, various techniques have been utilized for anatomical, electrophysiological, and biochemical augmentation of cortical reorganization, often termed neuronal plasticity [5].

In recent years, vagal nerve stimulators, both transcutaneous and implanted, have been used in combination with music therapy, tone pairing and rehabilitative training to reduce the perception of tinnitus [6–10]. In general, vagal nerve stimulation (VNS) works by activating the release of multiple neuromodulators, including acetylcholine, norepinephrine, serotonin, and brain derived neurotrophic factor inducing an overall antiepileptic effect [6,9]. Hence, the foundation of the mechanism of action of VNS on tinnitus is based on shifting neural plasticity as previously demonstrated in animal models [11]. Engineer et al. have performed series of experiments on noise-exposed rats demonstrating that repeatedly pairing single and ranged tone frequencies with VNS stimulation leads to long-lasting changes in the cortical map driven by neural plasticity [11,12].

Transcutaneous and implanted VNS systems have now been used to modulate tinnitus in humans as well [13,14]. In these studies, the use of VNS was distinctly different to the traditional use of the device, as the stimulation was paired with specific sensory input rather than the unpaired impulse therapy that is utilized for treatment of epilepsy. Reduced subjective tinnitus intensity and/or awareness have been noted in some patients [7,13].

In this study, we retrospectively review the effect of VNS on comorbid perception of tinnitus in epilepsy patients. Given the large patient population that undergoes VNS implantation at our medical center, we explore the incidence of tinnitus in patients requiring implantation of VNS for medically refractory seizures. We further asked patients to quantify post-operative tinnitus after use of VNS alone without additional targeted tone treatment. We hypothesized that the

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effect will be somewhat limited, as prior animal studies have indicated that therapeutic VNS-tone pairing, outside of the tinnitus frequency is needed for perceived tinnitus reduction [11,12,15].

2. Patients and methods

After Institutional Review Board approval, a retrospective review of patients who underwent vagal nerve stimulator placement for medically-refractory epilepsy was performed. All patients who were operated on between January 2012 and February 2017 were included in the analysis. Patient charts were identified via a billing database, and a search of the electronic medical record was performed. A total of 280 patients were initially identified. Inclusion criteria consisted of age older than 18 years old, competency to consent for procedures, current use of VNS, and active current contact information. Exclusion criteria included lack of mental capacity, inactive patient account, and removal/deactivation of VNS. After the application of the inclusion and exclusion criteria a total of 126 charts were selected for further review. Demographics, medical comorbidities, and postoperative complications were collected to facilitate data stratification. A phone survey was completed with a response rate of 44%, resulting in a total of 56 patients whose data was further analyzed. The aim of the phone survey was to retrospectively determine the presence of tinnitus in patients prior to vagal nerve stimulator placement. Given the retrospective nature of this component of the survey, a simple yes/no question regarding presence of pre-operative tinnitus was asked. With a negative response the phone survey was ended. If the patient acknowledged pre-operative tinnitus (n = 20), a series of follow-up questions were asked. The visual analog scale (VAS) of tinnitus loudness (a 10-point scale where 0 = no tinnitus and 10 = the loudest tinnitus imaginable) was utilized to address pre- and post-operative tinnitus. The VAS of tinnitus loudness was utilized to minimize recall bias in more complex questionnaires. Additionally, the Tinnitus Handicap Index (THI), a well-recognized and validated questionnaire, was employed in patients who noted current presence of tinnitus. Patients were additionally asked about other tinnitus treatments that they have tried to implement or were currently using. Due to the varied nature of neurologic follow-up, VNS settings were not consistently recorded or known to most patients. For statistical analyses, categorical comparisons were performed using Chi-Squared and Welch's *t*-test as appropriate. Statistical significance was assumed for a p-value < 0.05.

3. Results

Out of the 56 patients who had completed the phone survey, 20 (35%) had pre-operative tinnitus. The average age of the surveyed cohort and the tinnitus positive group was 44.2 years and 52.8 years, respectively. The tinnitus positive group was significantly older ($p = 0.019$). There was no statistical difference in gender or race. One patient noted a post-operative complication of transient hoarseness, a well-documented complication of VNS surgery. No permanent vocal cord paralysis was noted. Out of the 56 patients, 14 have undergone battery replacement since initial surgery, all without any further complications. Tinnitus positive patients' demographics are listed in Table 1. Major depressive disorder (MDD) was noted in 18 (32.1%) patients of the surveyed cohort and in 6 (30%) of the tinnitus positive group.

Of the 20 pre-operative tinnitus positive patients, all patients continued to have tinnitus post-operatively. Four (20%) noted no changes in VAS of tinnitus loudness while 16 (80%) had at least a one-point decrease. No patient noted increased VAS of tinnitus loudness (Fig. 1). The mean pre- and post-operative VAS of loudness were 5.85 and 3.80, respectively. The mean difference between pre- and post-operative VAS of loudness was 2.05, with a standard deviation of 1.84 and this was statistically significant ($p < 0.001$).

Current THI scores of tinnitus positive patients are also listed in Table 1. The average score was 41.75, for post-VNS treatment after scaling adjustment. There was a strong positive correlation, passing normality, with correlation coefficient equal to 0.910 ($p < 0.001$); Table 2 summarizes these results.

4. Discussion

In this study, we show that VNS alone has the potential to decrease the severity of subjective tinnitus in a specific subset of patients. Patients with refractory epilepsy create a rare subgroup of interest. Advances in the understanding of tinnitus pathophysiology reveal many similarities with other disorders of the central nervous system, such as epilepsy, posttraumatic stress disorder or affective disorders [16]. This link is thought to be due to neuronal hyperexcitability, serving as a potential catalyst for both epilepsy and tinnitus. This correlation has been a new topic of research as specific channel activators can suppress in vivo epileptic activity and prevent the development of tinnitus [16]. Ultimately, there is not a well-documented correlation between tinnitus and epilepsy; however, our findings of tinnitus in 35% of the patient population is significantly higher that what is quoted for general population [1,2]. Interestingly, MDD was noted to be a common comorbidity in both the overall cohort and the tinnitus positive group with incidence of 32.1% and 30%, respectively. Depression is the most frequent comorbid psychiatric disorder in epilepsy with published incidence of mood disorders in epilepsy ranging from 11 to 62% [17].

Along with the significantly higher incidence of tinnitus in our patient population, most patients who endorsed pre-operative tinnitus reported a statistically significant decrease in the intensity after placement of a vagal nerve stimulator. In contrast to prior studies, we did not use tone pairing or other concomitant treatment to augment tinnitus treatment. Current research suggests that VNS paired with tones or with rehabilitative training can help patients to achieve reductions in tinnitus perception or to expedite motor rehabilitation after suffering an ischemic stroke [8]. In a series of twenty-one stroke patients, the group that was randomized to VNS plus rehabilitation vs rehabilitation alone showed that paired VNS therapy is feasible with no safety concerns [18]. The general rationale behind gradual tinnitus reduction with VNS paired experience is neuronal plasticity in a controlled and therapeutic direction [8,12]. Initial animal tests have shown that repeatedly pairing tones with brief pulses of VNS reversed the physiological and behavioral correlates of tinnitus in noise exposed rats [11].

In a more recent clinical trial by Tyler et al., patients with refractory tinnitus were implanted with vagal nerve stimulators and either provided paired stimulus tone therapy or no additional therapy for 6 weeks [7]. This study provided the first prospective human evidence in support of the hypothesis that pairing VNS with stimulus tones drives neuronal plasticity associated with a reduction in the tinnitus percept. Of the thirty participants, 67% routinely used the device through the twelve months. At one year, 50% of participants had a clinically meaningful response [7].

Paired tone VNS has also shown successful results when used transcutaneously. Various end branches instead of the main vagal trunk can be stimulated in such fashion. There are currently clinical trials underway specifically targeting the auricular branches with and without paired tones with goals of tinnitus reduction [9,19]. In a small case series of 10 patients who had undergone serial transcutaneous VNS with sound therapy, the treatment group noted a statistically significant improvement in mood and decreased tinnitus severity as measured by THI scores [20]. The combination of these results is in accordance with our results of decreased VAS of tinnitus and THI.

As the body of literature regarding the utilization of VNS for treatment of tinnitus expands, more data will be available to understand the potential for a direct correlation between sound pairing, frequency of stimulation and areas of brain specifically affected during such episodes. Data regarding EEG recording during paired tone VNS stimulation suggests a reduction in gamma band activity in left auditory