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Efficacy of caloric vestibular stimulation for the treatment of idiopathic tinnitus

İdiyopatik tinnitus tedavisinde kalorik vestibüler stimülasyonun etkinliği

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Abstract

Aim: Caloric vestibular stimulation (CVS) induces the activation of several cortical structures and has been utilized as a neuromodulation technique in the treatment of several disorders. This study purposed to investigate whether CVS would be beneficial in the management of idiopathic tinnitus.

Methods: Patients with unilateral idiopathic tinnitus were enrolled in the study. CVS with cold water (study group) and body temperature (control group) irrigation were applied to the symptomatic ear. All patients underwent a standard audiometric examination and visual analogue scale (VAS), the tinnitus handicap inventory (THI) and the Beck depression inventory (BDI) were administered.

Results: VAS intensity and disturbance values, mean THI and BDI scores did not show any significant changes in the control group. In the study group, a significant improvement in both the tinnitus intensity and disturbance occurred in the first week post-intervention (P<0.001), and a significant decline was observed in median THI and BDI scores as well as the loudness of the tinnitus in the four weeks post-CVS (P<0.001, P<0.001, P=0.004 and P=0.001) respectively).

Conclusion: We can conclude that CVS with cold water leads to a significant decline in the intensity of tinnitus and reduction in the loudness of tinnitus, as well as improving THI and BDI scores.

Keywords: Caloric vestibular stimulation, Cold, Idiopathic tinnitus, Neuromodulation, Tinnitus Handicap Inventory

Öz

Amaç: Kalorik vestibüler stimülasyon (KVS), kortikal yapıların aktivasyonunu indükler ve çeşitli hastalıkların tedavisinde bir nöromodülasyon tekniği olarak kullanılır. Bu çalışma, KVS'nin idiyopatik tinnitus tedavisinde yararlı olup olmayacağını araştırmayı amaçlamıştır.

Yöntemler: Tek taraflı idiyopatik tinnitusu olan hastalar çalışmaya alındı. Semptomatik kulağa soğuk su (çalışma grubu) ve vücut ısısında su (kontrol grubu) olmak üzere KVS irrigasyonu uygulandı. Tüm hastalara standart odyometrik muayene yapıldı ve görsel analog skala (GAS), tinnitus engellilik anketi (TEA) ve Beck depresyon anketi (BDA) uygulandı.

Bulgular: Tinnitus şiddeti ve rahatsız olma GAS değerleri, ortalama TEA ve BDA skorları kontrol grubunda anlamlı bir değişiklik göstermedi. Çalışma grubunda müdahale sonrası ilk haftada hem tinnitus şiddeti hem de rahatsız olma skorlarında anlamlı iyileşme oldu (P<0,001). Çalışma grubunda KVS sonrası dört hafta içinde medyan TEA ve BDA skorlarında ve tinnitus sesinde anlamlı düşüş gözlendi (sırasıyla P<0,001, P<0,001, P=0,004 ve P=0,001).

Sonuç: Soğuk su ile yapılan KVS'nin, tinnitus yoğunluğunda önemli bir düşüşe ve tinnitusun ses şiddetinde azalmaya yol açtığı ve ayrıca TEA ve BDA skorlarını iyileştirdiği sonucuna varabiliriz.

Anahtar kelimeler: Kalorik vestibüler uyarı, Soğuk, İdiyopatik tinnitus, Nöromodülasyon, Tinnitus engellilik anketi

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Introduction

Tinnitus is defined as the perception of sound in the absence of an acoustic stimulus. It affects up to 18% of the general population to some extent in industrialized countries, and 0.5% of the patients with tinnitus describe severe disability precluding their ability to lead a normal life [1]. The pathophysiology of tinnitus is heterogeneous and incompletely understood; however, recent evidence indicates that it may result from abnormal neural activity and maladaptive plasticity in response to hearing loss [2]. All levels of the auditory pathways and several non-auditory systems are considered to act in the development and maintenance of tinnitus, with the prepotency of non-auditory systems in determining the level of annoyance of the tinnitus [3]. Several diseases, including age-related hearing loss, Menière's disease, noise-induced hearing loss, acoustic neuroma, depression, chronic otitis media, barotraumas, head injuries, and drug intoxications such as aspirin or quinine toxicity, have been shown to contribute to the development of tinnitus [1].

Various agents including melatonin, lidocaine, antidepressants, anticonvulsants, and anxiolytics have been studied for the medical treatment of tinnitus [4]. The abnormal neuronal activity observed in patients with tinnitus led to the application of neuromodulation methods for its treatment. For this purpose, transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) have been employed in the management of tinnitus. In both single and repeated sessions, tDCS interventions have shown beneficial results in tinnitus symptoms and depression and anxiety comorbid with tinnitus [5]. It has been observed that active rTMS administration of 1-Hz rTMS daily over ten consecutive workdays causes a decrease in tinnitus compared to placebo [6]. However, the treatment of tinnitus is problematic as a scientifically validated medication or cure has not been defined yet.

Caloric vestibular stimulation (CVS), which requires the application of cold or warm water into the external ear canal, has traditionally been a routine diagnostic technique in the neurological assessment of vestibular function. CVS induces activation of a number of cortical structures including the posterior insular and retroinsular cortices, temporoparietal junction, inferior parietal lobule, somatosensory area, parietal operculum, and superior temporal gyrus[7]. CVS was utilized as a neuromodulation technique in the treatment of post-stroke hemineglect, severe chronic pain, hemianesthesia, and bipolar disorder [8].

Implementation of CVS in the suppression of tinnitus was first described by Lamprecht et al. three decades ago [9]. The authors demonstrated that application of warm water (44ºC) into the ear canal was associated with an increase, while the cold-water irrigation (30ºC or 23ºC) caused a decrease in the loudness of the tinnitus. However, another study with 19 patients failed to demonstrate any impact of CVS on the modulation of tinnitus [10]. The conflicting results obtained in previous studies necessitate further research to clarify the role of CVS in the management of tinnitus.

Therefore, in this study, we aimed to investigate whether cold CVS can be beneficial in the management of tinnitus and improve the self-reported disability of the patients associated with tinnitus.

Materials and methods

The study was approved by the Istanbul Medipol University Ethical Committee (10840098-604.01.01-E.991 04/05/2018) and was performed in accordance with the recent version of the Helsinki Declaration. Written informed consent was obtained from all subjects included in the study. The power calculation was based on our pilot study with the first 15 patients. We used paired t-tests to assess the difference between two dependent means for VAS intensity (Pre-treatment: 6.2 (2.3), Post-treatment: 4.6 (1.8), alpha error: 0.05, power: 0.95, effect size: 0.76). Results revealed that at least 20 patients and 20 controls were required for adequate sample size [11].

Patients and Controls

All consecutive patients with the complaint of tinnitus who were admitted to the outpatient clinic of the otorhinolaryngology department of a tertiary center between May 2018 and June 2020 were prospectively enrolled in this study. Detailed medical history was obtained from all participants. All study patients underwent a complete audiological, ontological, and neurological examination to rule out the potentially treatable causes of tinnitus. Blood samples were drawn for complete blood count, serum biochemistry, vitamin B12 levels, thyroid function tests, and erythrocyte sedimentation rate. All patients underwent a standard audiometric examination, pure-tone audiometry, and speech audiometry with a clinical audiometer device in soundproof booths (AC40, Interacoustics, Middelfart, Denmark), and conventional tympanometry (Interacoustics AT235, Denmark). Pitch match frequency and loudness analyses of tinnitus were done for all patients on admission and four weeks after CVS. Advanced examinations such as contrast-enhanced temporal bone or cranial magnetic resonance imaging were requested when required.

A total of 50 patients with idiopathic tinnitus who met the below criteria (mean age 51.3 (8.6) years, minimum 26 – maximum 70 years, 50% male) were enrolled in this study. Thirty patients (15 women and 15 men) who came to our outpatient clinic with the complaint of tinnitus and met the below criteria were identified as the control group (mean age 54.3(8.3) years, minimum 33 – maximum 69 years).

Inclusion criteria:

1. Patients aged between 18 and 75 years.
2. Patients with unilateral tinnitus ongoing for at least six months who had received medical treatment for tinnitus for at least two months and had been refractory to medical treatment, had been free from any kind of medical agents prescribed to relieve the tinnitus for the last three months, and had been diagnosed with non-pulsatile subjective tinnitus.
3. Patients with full capability of communication.

Exclusion criteria:

1. Patients younger than 18 years and older than 76 years.

2. The presence of peripheral or central vestibular disease, cardiovascular disease, previous head trauma, neurological disease, metabolic disease, pregnancy, acute or chronic ear infection, and history of ear surgery.
3. Patients without full capability of communication.

Caloric vestibular stimulation

Study Group

CVS was performed in a 30º head-up position, with the head turned away from the ear being irrigated. Frenzel's goggles were applied to ease the observation of the nystagmus and to avoid fixation. The ear canal of the symptomatic ear was filled with 5-10 ml of cold water (4ºC) [12]. Nystagmus beats occurred approximately 30 seconds after the delivery of cold water and continued for the ensuing 30-45 seconds. In order to avoid post-CVS lightheadedness and nausea, subjects were kept in semi-recumbent position until nystagmus terminated.

Control Group

CVS was performed in 30º head-up position, with the head turned away from the ear being irrigated. Frenzel's goggles were applied to ease the observation of the nystagmus and to avoid fixation. The temperature of the ear canal of the symptomatic ear was measured, then the water was warmed to that degree Celsius, which was in the range of 36.0-36.8ºC. The ear canal was filled with 5-10 ml of water at body temperature as sham procedure. The emergence of nystagmus was inspected for a minute, and once there was no nystagmus, the patient returned to sitting position.

Assessment of tinnitus

A visual analog scale (VAS) was used in the assessment of the tinnitus before CVS (baseline) and repeated one week and one month after the application of CVS. The assessment was carried out in relation to intensity and disturbance. All tinnitus patients were asked to assign a 0 to 10 score to their tinnitus, with the help of a proper ruler (0 points being most favorable and 10 points being least favorable).

Tinnitus Handicap Inventory

The Tinnitus Handicap Inventory (THI) was used to address the disability experienced by the patients due to tinnitus before and four weeks after the application of the CVS. THI is a 25-item questionnaire that probes the functional, emotional, and catastrophic response reactions to tinnitus. Each item of the THI is ranked from 0 to 4 to build up a total score between 0 and 100 points. The THI score of 0–16 means "no or slight handicap", 18–36 indicates "mild", 38–56 indicates "moderate", 58–76 indicates "severe", and a score of 78–100 is classified as "catastrophic handicap" [13].

Beck Depression Inventory

Beck Depression Inventory (BDI) was used in the evaluation of the depressive symptoms before and four weeks after the application of the CVS. BDI is an instrument used for the purpose of diagnosing depression. It consists of 21 items on symptoms and attitudes, with intensities ranging 0-3 [14]. The items refer to sadness, pessimism, sense of failure, lack of satisfaction, guilt, feeling of punishment, self-deprecation, self-accusation, suicidal ideation, crying spells, irritability, social withdrawal, indecisiveness, distortion of body image, inhibition to work, sleep disorder, fatigue, loss of appetite, weight loss, somatic concern, and decreased libido. A BDI score of ≥16 indicates depression, while lower scores address non-depressed individuals.

Statistical analysis

Statistical analyses were carried out using SPSS for Windows, version 21 (SPSS, IBM Corp., Armonk, N.Y., USA). Shapiro–Wilk test was used to check the normality of the variables. Continuous variables are presented as mean (standard deviation (SD)) and categorical variables as frequency (n) and percentage (%). Paired samples t-test and repeated measures ANOVA were employed in comparison of pre- and post-interventional VAS scores and tinnitus frequency and loudness (normally distributed data). The comparison of the pre- and post-interventional THI and BDI scores was performed with the Wilcoxon signed-rank test. Pearson and Spearman correlation analyses were performed to identify the association between the THI score and BDI score before and after CVS. A two-sided P-value ≤0.05 was interpreted as statistically significant.

Results

Demographic characteristics and the clinical features of the study and control subjects are presented in Table 1. The symptomatic ear that received CVS treatment was the right ear in 19 (38%) subjects and the left ear in 31 (62%) subjects in the study group, and the right ear of 15 (50%) and left ear of 15 (50%) subjects in the control group. Except for lightheadedness in a few patients, CVS was well tolerated and no complications were recorded during or after the procedure. The distributions of gender, age, and the results of basal audiometric tests and basal self-report questionnaires were not significantly different (P>0.05) between the study and control groups.

Table 1: Demographic characteristics and clinical features

Variables	Study Group Mean (SD)	Control Group Mean (SD)	P-value
Age,years	51.3 (8.9)	54.3 (8.3)	0.08
Gender			$\chi^{(chi)2}$:0.00;
Male, n	25 (50 %)	15 (50 %)	df:1;
Female, n	25 (50 %)	15 (50 %)	p=1.0
Tinnitus duration, years	4.1 (3.0)	3.1 (2.0)	0.234
R AC threshold	27.5 (9.2) dB	26.6 (13.3) dB	0.661
R BC threshold	21.2 (8.1) dB	21.9 (11.3) dB	0.936
L AC threshold	30.8 (9.2) dB	26.5 (13.5) dB	0.94
L BC threshold	23.3 (6.9) dB	22.5 (11.6) dB	0.526

AC: Air Conduction, BC: Bone Conduction, R: Right, L: Left

The changes in the VAS ratings of the tinnitus from the baseline to four weeks post-CVS are presented in Table 2. VAS intensity and disturbance values did not show any significant changes in the control group. However, significant improvements in both the intensity and disturbance occurred from baseline to the first week post-intervention in the study group (P<0.001). VAS intensity and disturbance values had complete improvement one week after treatment in 12 patients. Although intensity and disturbance were still more favorable than the baseline values (P<0.001) and different from the controls (P<0.001), in the study group, impairment was observed in both intensity and disturbance from the first week post-CVS to the first month post-CVS. Moreover, a significant decline was observed in median THI [48 (14-96) points vs. 40 (8-84) points, P<0.001] and BDI scores [13 (2-42) points vs. 8 (1-29) points, P<0.001] from baseline to the first month post-CVS in contrast to the controls, who were unchanged (Table 3). The mean BDI score was strongly correlated with the mean THI score before and after CVS in both the study group (r=0.846, P<0.001 and r=0.721, P<0.001, respectively) and controls (r=0.694, P<0.001 and r=0.700, P<0.001, respectively).

Table 2: Change in the VAS score of the intensity and disturbance arising from the tinnitus from baseline to the post-treatment one month in each group and between the groups

	Study Group				Control Group				
	Baseline (mean (SD)	1st week (mean (SD)	1st month (mean (SD)	P-value*	Baseline (mean (SD)	1st week (mean (SD)	1st month (mean (SD)	P-value*	P-value**
VAS (intensity)	6.6 (2.2)[a]	3.1 (1.4)[b]	3.9 (1.9)[c]	<0.001	7.6 (1.7)	7.3 (1.6)	7.4 (1.8)	0.134	<0.001
VAS (disturbance)	6.5 (1.9)[a]	2.9 (1.2)[b]	3.4 (1.7)[c]	<0.001	6.7 (1.9)	6.6 (1.7)	6.6 (1.8)	0.184	<0.001

VAS: visual analogue scale. a,b,c: Same letters in the same row denote the lack of the significant difference between the two variables in the same row. Paired samples t-test, within each group, between the baseline and the first month measurements (p*). Repeated measures ANOVA (group×time×frequency), between the subject effects (p**).

Table 3: The comparison of BDI and THI scores between the pre-and post-CVS interventions in each group

	Study Group			Control Group		
	Pre- CVS	Post- CVS	P-value	Pre- CVS	Post- CVS	P-value
BDI score Median (min-max)	13 (2-42)	8 (1-29)	<0.001	8.5 (2-32)	9 (2-30)	0.490
THI score Median (min-max)	48 (14-96)	40 (8-84)	<0.001	43 (10-96)	44 (10-96)	0.106

CVS: Caloric Vestibular Stimulation, BDI: Beck Depression Inventory, THI: Tinnitus Handicap Index. P= Wilcoxon signed-rank test

Comparisons of pre-and post-CVS tinnitus frequency and loudness for the symptomatic ears within each group and between the groups are presented in Table 4. The loudness of the tinnitus displayed significant reductions in the symptomatic ear of the study patients following the intervention with CVS (P<0.05), whereas no significant change occurred in the frequency of the tinnitus (P>0.05). The change in tinnitus loudness by time was not significantly different from the controls, although there was almost no change observed in those patients.

Table 4: Comparison of pre-and post-CVS levels of tinnitus frequency and loudness for the relevant ear in each group and between groups

	Study Group (Mean (SD)			Control Group (Mean (SD)			
	Pre-CVS	Post-CVS	P-value*	Pre-CVS	Post-CVS	P-value*	P-value**
Tinnitus frequency R	5200 (2067)	4950 (2012)	0.096	5071 (1940)	4929 (1940)	0.336	0.914
Tinnitus frequency L	5356 (2125)	5266 (2099)	0.184	4125 (1360)	4125 (1360)	>0.999	0.047
Tinnitus loudness R	56.5 (13.86)	49.75 (16.89)	0.004	51.1 (13.47)	51.1 (13.75)	>0.999	0.682
Tinnitus loudness L	57.16 (12.15)	54.16 (12.46)	<0.001	57.81 (10.80)	57.19 (11.25)	0.164	0.617

CVS: Caloric Vestibular Stimulation, L:Left, R: Right, SD: Standard Deviation. Paired samples t-test, within each group, between the baseline and the first month measurements (p*). Repeated measures ANOVA (group×time×frequency), between the subject effects (p**).

Discussion

The present study clearly demonstrates that CVS with cold water at 4º C leads to a significant decline in intensity and disturbance of tinnitus as measured with the VAS for the symptomatic ear, compared to the CVS with water at body temperature. The implementation of CVS with water at 4º C also improves THI and BDI scores and decreases the loudness of the tinnitus. To the best of our knowledge, this is the first study that investigates the role of cold CVS in the modulation of idiopathic tinnitus.

The evidence derived from quantitative electroencephalography and neuroimaging studies indicates the involvement of both auditory and non-auditory brain areas in different aspects of tinnitus. The primary and secondary auditory cortices are, therefore, recognized as potential targets for the management of tinnitus [15]. Tinnitus may result from increased neuronal activity within the auditory cortex that develops due to the imbalance between excitatory and inhibitory mechanisms or an adjustment of auditory gain mechanisms [16]. The non-auditory brain areas involved in the pathogenesis of tinnitus include the anterior cingulate cortex, anterior insula, amygdala, orbitofrontal cortex, dorsal lateral prefrontal cortex, posterior cingulate cortex, the precuneus, and the hippocampal and parahippocampal areas [17, 18]. Increased activation of the bilateral superior temporal gyrus, which contains both primary and secondary associations with the auditory areas, have been observed during CVS in previous studies [19]. CVS has been shown to modulate vestibular nerve activity as a consequence of the induction of the endolymphatic flow in the inner ear. CVS might, therefore, affect auditory nerve activity through the participation of the superior temporal gyrus in an auditory–vestibular interaction [12]. The improvement in tinnitus-associated symptoms and audiological measurements accomplished with cold CVS in our study might be associated with the modulation of this multimodal vestibular network by the CVS.

Electrophysiological studies of auditory sensory gating in humans and animal models have demonstrated the involvement of the posterior parahippocampal area in auditory habituation [20,21]. Development of auditory hallucinations following the deactivation of the parahippocampal gyrus in patients with psychotic disorders supports the involvement of the parahippocampal area in auditory procession [22]. Thus, it has been considered that parahippocampal structures are critical in the establishment of auditory memory for tinnitus. In addition, the contralateral parahippocampal area is related to the lateralization of tinnitus [23]. The side of the stimulus is an important component of the cortical activation pattern. Positron emission tomography and functional magnetic resonance imaging studies demonstrated that application of cold CVS leads to contralateral activation in temporoparietal regions, whereas warm CVS leads to the ipsilateral activation of these regions [24]. From the perspective of our findings, we speculate that the hyperactivity of the contralateral parahippocampus in subjects with tinnitus might be rebalanced with the increase in the activity of the ipsilateral parahippocampal area through CVS.

Strong integration between the cortical vestibular system and somatosensory processing has been reported previously [25]. An alteration in the inhibitory effect of the dorsal cochlear nucleus may, therefore, result in tinnitus. Several pieces of research have documented the existence of interconnections from the somatosensory system to the dorsal cochlear nucleus, which may contribute to the development of the somatic tinnitus [26]. The dorsal cochlear nucleus receives input from the somatosensory system, in particular, from the external ear. Thus, the somatosensory inputs arising from the external ear with the application of CVS in our study might have also suppressed the symptoms of tinnitus through the network between the somatosensory system and the dorsal cochlear nucleus. We also consider that CVS application might have suppressed the perception of tinnitus by influencing the autonomic system, auditory system, facial nerve activity, and trigeminal nerve activity.

Among the non-auditory areas of the brain that are related to tinnitus, the limbic system and other forebrain regions have been the focus of a great number of studies. A bi-directional interconnection exists between the limbic system and the auditory system, and a large variety of brain functions and behaviors have been related to these interconnections [27]. The ventromedial prefrontal cortex and the nucleus accumbens have been documented to be the contributors to the generation and maintenance of tinnitus [28]. The hearing-loss induced hyperactivity in auditory circuits is ordinarily suppressed by the ventromedial prefrontal cortex and the nucleus accumbens; thus, the lack of the proper functioning of these structures may lead to inappropriate neural activity in the thalamus and result in tinnitus. Application of cold water into the external auditory meatus might play a modulatory impact on the interconnections presenting between the limbic and the auditory systems.

The present study demonstrates the positive effects of CVS with cold water on audiologic and self-reported quality measures of idiopathic tinnitus. CVS led to an acute improvement in the self-reported intensity and disturbance of the tinnitus despite the lack of a change in the frequency of the tinnitus. Although an increase in both the intensity and disturbance caused by the tinnitus was reported at the fourth week, it was still encouraging than the baseline scores. This was further supported by the improvement in the THI and BDI scores. Both THI and BDI demonstrate the impact of the tinnitus on the psychological state of the subjects. A possible explanation for the relationship between the depressive symptoms and the tinnitus might be that the 'distress circuit', which includes several limbic structures, contributes to the transition of the tinnitus percept to a distress response [27]. The present study documented the correlation between the BDI score and THI score in both arms. However, whether depression accompanies tinnitus or tinnitus is the cause of the high BDI scores is not clear. In addition, there might be a bidirectional relationship between depression and tinnitus. Further research is required to clearly address the cause-and-effect relationship between tinnitus and depression. In addition to these, although CVS with cold water was effective in tinnitus, CVS application at body temperature did not cause any improvement in tinnitus symptoms. There is no study using water at body temperature as we did in the control group. However, Baguley et al.[10] showed that CVS application with water at 44 ° C had no effect on tinnitus. Our findings in the control group are consistent with the study findings of Baguley et al.

Although the clear explanation of the pathophysiological mechanism of the benefit accomplished with CVS is beyond the scope of this paper, we suggest that modulation of neuronal hyperactivity among the complex interconnections existing between the non-auditory and the auditory structures is the most probable contributor of CVS to the suppression of tinnitus.

Limitations

The most important limitation of our study that needs to be improved is that we failed to demonstrate the functional and structural changes in the particular brain areas with either functional magnetic resonance imaging or electroencephalography during CVS. Thus, we cannot provide a clear topographic explanation to the question 'how does CVS with cold water eliminate or alleviate tinnitus?' More comprehensive studies, including imaging data, are required to accurately address the mechanism of the benefit derived from the CVS.

Conclusion

This study clearly shows that CVS with cold water leads to a significant improvement in symptoms associated with idiopathic tinnitus compared to CVS with water at body temperature. It can be speculated that the benefit derived from CVS is related to its modulatory effects on the cortical, thalamic, and limbic areas, and the neuronal network between the dorsal cochlear nucleus and the somatosensory system. More research is needed to identify the precise neuronal pathways affected by CVS and to observe its long-term effects.

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