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REVIEW ARTICLE

Transcranial direct current stimulation in treatment of tinnitus

Abdollah Moossavi[1], Sirvan Najafi[2*]

[1]- Department of Otolaryngology-Head and Neck Surgery, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
[2]- Department of Audiology, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran

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Abstract

Background and Aim: Approximately 20% of general population is struggling with tinnitus. Recent theories on tinnitus are mainly based on impairments in the central auditory system that can lead to tinnitus. Recent studies have shown that tinnitus is not simply a result of the involvement of one brain region or pathway; but it can be caused by simultaneous involvement of multiple brain regions. Due to lack of information about the tinnitus etiology, site, and pathophysiology, there is still no any specific and common method for its management. In recent years, neuromodulation techniques such as transcranial direct current stimulation (tDCS) has been proposed for management of tinnitus. In this study, we aimed to review the role of tDCS in tinnitus management.

Recent Findings: Based on the inclusion criteria, 7 eligible articles were selected for review. Most of them showed the beneficial effects of tDCS on tinnitus management.

Conclusion: The tDCS can be an effective technique for management of tinnitus. One of the main challenges for using tDCS in tinnitus patients is the differnce in stimulation parameters; therefore, more studies are recommended for obtaining its ideal parameters.

Keywords: Transcranial direct current stimulation; tinnitus; neuromodulation

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[*] **Corresponding author:** Department of Audiology, University of Social Welfare and Rehabilitation Sciences, Daneshjoo Blvd., Evin, Tehran, 1985713871, Iran. Tel: 009821-22180100, E-mail: sirwannajafi@gmail.com

Introduction

The term tinnitus originated from the Latin word "*tinnire*" which means to ring. Tinnitus is a perception of sound in the head or ears with absence of an external source [1]. Based on epidemiological studies, approximately 20% of people are struggling with tinnitus, indicating a high prevalence of tinnitus [2,3]. According to previous theories, dysfunction of the inner ear is involved in generation of tinnitus; however, recent studies have shown that tinnitus was not eliminated after bilateral removal of acoustic neuromas; hence, tinnitus may have a central origin [4]. Some theories about this problem are mainly based on the dysfunction in the central auditory system caused by receiving distorted auditory input leading to tinnitus [5]. Neuroimaging and electrophysiological studies have shown the increased spontaneous activities in the central auditory system and even some changes in tonotopic maps of tinnitus patients. Therefore, tinnitus can lead to neuroplastic changes in the brain [6]. Recent findings have shown that tinnitus is not simply caused by the involvement of one site or pathway; it can be caused by the simultaneous involvement of multiple brain regions like the auditory and somatosensory cortices, as well as

several parallel and overlapping networks involved in perception and reaction to tinnitus including memory (hippocampus, parahippocampal, and amygdala), perception (dorsal-anterior cingulate cortex, parietal cortex, and precuneus), salience (dorsal-anterior cingulate cortex), and distress (amygdala, anterior insula, and dorsal-anterior cingulated cortex) networks [7]. Hence, it can be assumed that tinnitus perception is the result of a wide range of networks with several overlapping subnets activated based on separate aspects of tinnitus like quality (ringing vs. noise), side effects, and distress [8]. Perceptual characteristics, symptoms, comorbidities, and pathophysiological mechanisms of tinnitus are not the same among patients and may change over time [9].

Several studies have shown that, although most people do not pay attention to tinnitus, the annoyance caused by tinnitus is extremely intense for 1% of them and may have a negative effect on their quality of life and lead to impairments in sleep, concentration, daily activities, or distress [10,11]. Due to lack of information about its etiology, site, and pathophysiology, there is not any specific method for its management [12]. Each proposed methods for its management has its own advantages and disadvantages [13]. Several studies have indicated the presence of abnormal excitability in the auditory pathways and even abnormal plasticity in cortical and limbic systems in tinnitus patients. These findings motivated researchers to use brain stimulation for the modulation of activities in the cortical areas [6,7,14]. Recent theories on the neuroscience of tinnitus have shown that neuronal changes are not merely related to the auditory pathways; areas such as dorsolateral prefrontal cortex (DLPFC) have an important role in tinnitus perception and auditory processing. In addition, DLPFC has a facilitating role in the auditory memory function [15]. According to electrophysiological studies, this part of the prefrontal cortex is important in inhibitory modulation of auditory input to the primary auditory cortex, and may be related to auditory attention, and effective in the top-down auditory processing [8].

Different methods have been proposed for the treatment of tinnitus with different results. This may be due to the non-uniformity in tinnitus generation and the non-uniform reactions of the nervous system and patients to this unpleasant phenomenon. In recent years, the use of the neuromodulation techniques such as repetitive transcranial magnetic stimulation (rTMS), neurofeedback, transcutaneous electrical nerve stimulation (TENS), and transcranial direct current stimulation (tDCS) for the treatment of tinnitus have become popular and successful in some cases [16]. De Ridder et al. showed that extracutaneous electrical stimulation of the auditory cortex could suppress tinnitus; however, the main drawback of their method was its electrical and invasive nature [17]. This challenge led to the use of non-invasive and minimally invasive techniques for the treatment of tinnitus. The tDCS is safe, affordable and less invasive comapred to other neuromodulation techniques such as rTMS. Since DLPFC is involved in auditory attention, tinnitus, and top-down inhibitory processes, it is logical to assume that tDCS is an appropriate technique for the management of tinnitus [18]. This technique has been studied and used extensively on various disorders as depression and schizophrenia [19]. It was introduced about 20 years ago for neurological purposes [20]; since then, it has been extensively applied for neuroplasticity and brain stimulation. It was first used by Fregni et al. [14] for the management of tinnitus. In this technique, a low-level direct electrical current is applied through the electrodes over the skull. Anodal tDCS causes increasing cortical excitability by inducing depolarization of the resting membrane potential, while cathodal tDCS decreases cortical excitability by hyperpolarization of the resting membrane potential [21,22]. Since DLPFC has a significant role in auditory processing and tinnitus, the tDCS is applied to this area in most studies. Many studies have shown that anodal tDCS on the right DLPFC decrease loudness and distress caused by chronic tinnitus, but anodal tDCS over the left DLPFC has shown no effectiveness [18]. In some studies, anodal tDCS over left temporoparietal area (LTA) caused transient suppression of tinnitus. It is proposed that the electrode array for tDCS

over the LTA stimulates many cortical and subcortical regions and, thus, results in decreased cortical hyperactivity in tinnitus patients [23,24]. In current paper, we aimed to review the role of tDCS in tinnitus management.

Methods

Data source

In this reviw study, the search was conducted in PubMed, Google Scholar, ScienceDirect and EMBASE databases from January 1, 2000 to February 25, 2019 by using "tinnitus", "tDCS" and "Transcranial direct current stimulation" keywords. Initial search yielded 2116 articles.

Study selection criteria

The inclusion criteria were: full-text availability of articles in English, clinical trials used tDCS only, the use of a sham or control group, the use of qualitative or quantitative scales before and after the treatment procedure, and patients' age >18 years. The abstracts, case reports, cohort studies, case series, and non-English articles were excluded from the review. Based on these criteria, 39 articles remained, consisting of 33 research articles (31 with full texts), 7 review articles, and one commentary article. The patients' characteristics (age, gender), tDCS parameters (electrode array, area of electrodes, number of sessions, and the intensity and duration of stimulation), and main results of these articles were reviewed. Based on these parameters, 7 articles were finally selected for review. The effectiveness of tDCS in tinnitus management was reported by Garin et al., Frank et al., Faber et al., Forogh et al. and Abtahi et al. [24-28], but such improvement was reported by Cavalcanti et al. and Pal et al. [29,30]. Due to the application of different parameters in these seven articles, we reviewed the effect of different parameters on the effectiveness of tDCS in tinnitus management.

Recent findings

As a total, 198 patients with a mean age of 49 years and a mean tinnitus duration of about 8 years were studied in the articles. The number of tDCS sessions was between 3−8 (mean = 6 sessions). Four of these articles used a current intensity of 2 mA, one used a 1 mA current, and two used a 1.5 mA current. Duration of stimulation was 20 minutes in six articles and 30 minutes in only one article. In active and sham tDCS groups of these articles, a visual analog scale (VAS) was applied before and after the stimulation. Tinnitus loudness and distress was assessed by the VAS in 7 and 5 studies, respectively. The VAS is a subjective scale that describes the severity of disease from 0 to 10, where 0 indicates no disease and 10 shows a severe level of disease [31]. VAS for is a reliable tool for assessing tinnitus loudness and distress, and a reduction in severity by 30% is ian indicative of improvement in symptoms [32]. Three studies reported a reduction in tinnitus loudness by VAS after tDCS [24,25,28]. In all studies, VAS results were significantly different before and after tDCS. The mean score of improvement was 36.87%. In other studies, no significant difference was reported. In 5 studies, researchers assessed tinnitus distress by VAS, in addition to tinnitus loudness. The distress-related VAS in studies by Garin et al., Frank et al., and Faber et al., results showed a significant difference between before and after tDCS [24-27,30], but in studies by Pal et al. and Forogh et al., no significant difference was reported.

In addition to the VAS tool, the tinnitus handicap inventory (THI) and tinnitus questionnaire (TQ) were used [33,34]. THI is a self-assessment psychometric scale of handicap perceived by a person with tinnitus. The final THI score is in a range of 0 to 100; the higher score indicates the higher level of handicap in the patient [33]. TQ is a tool for evaluation and differentiating between emotional, cognitive problems and auditory perception difficulties experienced by tinnitus patients. It can be used to measure the usefulness of different treatment options [34]. It has 52 items indicating the level of agreement between participants on a scale as: 0 = not true, 1 = partly true, and 2 = true. The total TQ score ranges from 0 to 82, with higher scores indicating higher tinnitus distress [35]. Results of Frank et al., Forogh et al., and Cavalcanti et al. [25,27,29] showed no significant difference in THI scores

Table 1. Summary of the general data and main results of seven studies that were included in the current paper

Authors and year of publication	Published year	Electrode array	Intensity, Duration	Area of electrodes	Measurement tools	Main results
Garin et al. [24]	2011	Anode on left LTA/cathod between T4 and F8	1 mA, 20 min	35 cm^2 50 cm^2	Loudness VAS/Distress VAS/TQ/BDI	Anodal and cathodal tDCS over LTA made change of loudness perceived by patient. Rate of improvement was better in anodal tDCS.
Frank et al. [25]	2012	Anode on right DLPFC/cathod on left DLPFC	1.5 mA, 30 min	NR NR	Loudness VAS/Distress VAS/TQ/BDI/ THI	Bifrontal stimulation by tDCS has little effect on loudness and distress. The impact of tDCS is gender-specific, so that women improvement more than men.
Faber et al. [26]	2012	In six cases anode on right DLPFC/in nine cases anode on left DLPFC	1.5 mA, 20 min	35 cm^2 35 cm^2	Loudness VAS/Distress VAS/HADS	Bifrontal stimulation by tDCS was effective on distress, but ineffective on loudness. Anodal tDCS over right DLPFC changes the anxiety of the patients and anodal tDCS over left DLPFC changes the depression.
Cavalcanti et al. [29]	2015	Anode on right DLPFC/cathod on left DLPFC	2 mA, 20 min	35 cm^2 35 cm^2	Loudness VAS/THI	Multi-session stimulation with tDCS has no significant effect on VAS and THI.
Pal et al. [30]	2015	One anode on prefrontal (Fz, F3, F4)/two cathods on T3 and T4	2 mA, 20 min	75 cm^2 35 cm^2 35 cm^2	Loudness VAS/Distress VAS/HADS/ CGI/STSS	Provide a five-session anodal tDCS to the DLPFC and cathodal to the AC, does not improve the tinnitus.
Forogh et al. [27]	2016	Anode on left LTA/cathod on right supra orbital	2 mA, 20 min	35 cm^2 35 cm^2	Loudness VAS/Distress VAS/THI/CGI	Multi-session tDCS over LTA has relatively improvement on loudness and distress VAS, althtough was not significant.
Abtahi, et al. [28]	2018	Anode and cathod positioned on T3 or T4	2 mA, 20 min	235 cm	Loudness VAS	Anodal tDCS was more effective in tinnitus patient (than cathodal or sham tDCS).

LTA; left temporoparietal area, mA; milliampere, min; minutes, cm^2; square centimeters, VAS; visual analogue scale, TQ; tinnitus questionnaire, BDI; Beck depression inventory, tDCS; transcranial direct current stimulation, DLPFC; dorsolateral prefrontal cortex, NR; not reported, THI; tinnitus handicap inventory, HADS; Hospital Anxiety and Depression Scale, CGI; clinical global impression scale, STSS; Subjective Tinnitus Severity Scale, AC; auditory cortex

before and after of tDCS. A statistically significant decrease in TQ scores was found in Garin et al.'s study [24], but it was not significant in Frank et al.'s study [25]. In some studies, except the reviwed ones, Beck Depression Inventory and Clinical Global Impression Scale have also been used, but no significant difference has been found in the scores before and after tDCS. The main results of seven reviewed articles are summarized in Table 1.

Discussion

Seven articles, in line with the current study purpose, were selected for review. Authors of these seven articles claimed that treatment modalities such as sound therapy, hearing aids, etc had no effect on tinnitus patients. They mentioned different etiologies for tinnitus such as

noise-induced hearing loss, presbyacusis, etc. and they reported no any correlation between a specific etiology and improvement caused by tDCS. Patients who received tDCS treatment had not benefited from other treatment options. Five articles showed some beneficial effects of tDCS on tinnitus treatment [24-28], indicating that tDCS could improve tinnitus in some patients according to the used questionnaires and the VAS. The improvement rate was different between studies; maybe because of the heterogeneity of study population and tDCS protocol. Two other studies reported no improvement. The site of stimulation selected in these studies was different. In three studies, the anode was positioned over the left LTA; in three studies, placed on the right DLPFC; and in one study, the anode was placed on prefrontal cortex and two cathodes over T3 and T4. Each study had its own reason for selecting the site of stimulation; however, most of them showed relative improvement in tinnitus patients without any considerable difference between the results. One reason for researchers to stimulate DLPFC, according to Vanneste et al. [18], was that DLPFC may play an important role in anxiety, depression, and unpleasant sensations such as pain. The activity of DLPFC is related to the emotional perception of pain, and may be correlated to the annoyance caused by tinnitus. DLPFC regulates the activity of regions involved in the emotional perception of tinnitus, including anterior cingulate cortex, insula, and amygdala. In this regard, it can be concluded that the bilateral stimulation of DLPFC and anterior cingulate cortex may be effective in controlling the perception of tinnitus. Anterior cingulate cortex has an important role in the emotional control of sensory processing. As top-down inhibitory signals originate in the prefrontal cortex, the anterior cingulate cortex can have an important role in auditory processing and tinnitus. Therefore, it is possible that bilateral stimulation of DLPFC by tDCS method affects top-down inhibitory processing in tinnitus and induce auditory sensory gating in the anterior cingulate cortex. Moreover, tDCS may be effective in reducing tinnitus distress by modulating the cortico-subcortical and cortico-cortical pathways [18]. However, this claim has not been proved in other studies. Shekhawat et al. believed that LTA must be stimulated by tDCS [36] because the lower part of left LTA consists of an important neural network affecting Brodmann areas 41 and 42 (primary auditory cortex), Brodmann areas 21 and 22 (associated auditory cortex) and limbic system (hippocampus and amygdala). Hence, it is reasonable that the stimulation of this region can directly affect the tinnitus perception and, finally, induce inhibition activities and suppress tinnitus, although its effect is not stable [36].

Another challenging issue was the polarity of electrodes. As mentioned before, anodal tDCS causes depolarization of the resting membrane potentials, while cathodal tDCS decreases cortical excitability by inducing hyperpolarization of the resting membrane potentials [21]. In most studies, it has been shown that the use of anodal tDCS leads to better improvement of tinnitus compared to cathodal tDCS [25,29,30]. The increase in cortical excitability caused by anodal tDCS may be aganist this claim that tinnitus is a result of increased excitability in some parts of the cortex. However, Fregni et al. proposed a solution for this ambiguity. According to them, the size of electrodes should be 35 cm^2 or more; as a result, a large area of the temporoparietal cortex is simultaneously stimulated in addition to the target region. Therefore, the excitability induced by anodal tDCS may activate surrounding areas through inhibitory neuronal connections and cause the defocusing effect of anodal tDCS on network activity. Decreased hyperactivity thus ends tinnitus and causes a transient improvement [14]. Joos et al. suggested higher current intensity for the cathodal tDCS in order to have effect equal to that of anodal tDCS [37]. Imaging and electrophysiological studies have shown that tinnitus patients have abnormal gamma band activity. Since the tinnitus loudness is correlated with gamma band in the contralateral auditory cortex, the anodal tDCS with its inhibitory effects may reduce the hyperactivity and loudness of tinnitus [6]. However, Joos et al. did not report such result, and recommended that other pathological mechanisms should be studied to justify this result [37]. A possible reason is that both anodal

and cathodal tDCS interferer with the brain networks activities. A study has shown that a 2 mA intensity of tDCS inverses the effect of cathode and leads to increased excitability [37]. The effect of tDCS duration and intensity on tinnitus need to be discussed. Although Shekhawat et al. found that the increase in both duration and intensity of tDCS was effective in improvement of tinnitus; however, the ideal duration and intensity still need to be found [36].

All the seven reviewed articles had a sham tDCS group and the active tDCS in five articles showed superior results compared to sham tDCS, although the difference was not statistically significant in two papers. In most of these studies, the parameters of stimulation were set in such a way that patients were not able to recognize whether they were receiving an active tDCS or a sham tDCS; for example, short but ineffective pulses were applied in sham group to cause an itching sensation like the sensation caused by active stimulation. Garin et al. talked to their patients during stimulation to distract them from the applied stimulation type. Interestingly, some patients showed an improvement by sham tDCS, may be because the patients did not recognize the type of stimulation [24]. In two studies, application of tDCS on the patients with tinnitus did not lead to any significant improvement [29,30]. Regarding the parameters used in these two studies, no association was found between brain stimulation parameters and tinnitus improvement.

The studies used multi-session tDCS showed a higher rate of tinnitus improvement than those perfomed tDCS in a single session. This may be due to difference in patient charactersitics and pathophysiological machanisms [29]. However, the superiority of multi-session tDCS over single-session tDCS is not a general rule [30]. The main reason is that multiple stimulation of a specific brain region has not shown any superior effect on tinnitus improvement [30]. The tDCS effect is almost the same as the rTMS effect; the tinnitus patients with no improvement by single-session rTMS, had a lower chance for improvement by single-session tDCS [25].

In the seven reviwed studies, the effect of tDCS was measured with different methods, including the VAS. Tinnitus loudness assessment by the VAS showed contradictory results in these studies; in two studies, the VAS results showed a reduction in tinnitus loudness while such effect was not reported in other five studies. Tinnitus distress assessment by the VAS had also contradictory results. One possible reason may be the subjective nature of the VAS; this method highly depends on the psychological and mental state of patients. There was a high correlation between assessment by the VAS and psychometric evaluation by TQ. The TQ may survey the daily living activities of patients and psychological aspects of tinnitus; therefore, psychometric evaluation by TQ may be a reasonable alternative to the VAS [38]. The effectiveness of tDCS was assessed by the THI and/or TQ in four studies. The scores of these questionnaires showed an improvement of about 30% in patients. Therefore, it seems reasonable to assess the outcome of tinnitus treatment with more than one method [39]. It is noteworthy that decreased score of questionnaires such as TQ may be due to the "Hawthorne effect". According to this effect, improvement of patient condition may be due to attendance in the study and follow-up phases [40].

The hearing status in tinnitus patients can affect the results of tDCS. Fregni et al. found that patients with better responses to tDCS had a better hearing status than those with poor responses. This may be due to higher neuroplastic changes in tinnitus patients with severe hearing loss compared to those with better hearing status. They concluded that a higher duration and intensity of tDCS may be needed for therapeutic effects in patients with severe hearing loss [14]. Based on the results of Frank et al., tDCS on seven female patients showed better results than on 25 male patients; therefore, they suggested the consideration of gender effect on tDCS. This effect became more pronounced when electrodes were positioned over the occipital, temporal, and frontal brain areas [25]. Since auditory and emotional processing is gender-related and females are more susceptible to aversive noises, they have different neuronal response in cognitive processes compared to males [41]. Therefore, gender differences should be considered

when designing and analyzing the effect of tDCS on tinnitus patients, especially when the frontal cortex is stimulated [25]. In six studies, tDCS exacerbated tinnitus mostly when the left LTA was stimulated. This exacerbation should be considered as one of the side effects of tDCS. It may not be correct to relate this issue to tDCS; however, such exacerbation may indicate that tDCS can change the neuroplasticity of these patients. Therefore, it can be expected that, by altering the parameters and achieving ideal ones, tDCS can improve tinnitus [27].

Conclusion

The tDCS can be an effective modality for the management of tinnitus. Despite the low rate of tinnitus improvement reporetd in the reviewed articles, tDCS can be a promising method for the tinnitus patients who have not benefited from other management modalities. One of the main challenges of using tDCS for the management of tinnitus is the differnces in stimulation parameters. Therefore, more studies are recommended for obtaining its ideal parameters.

Conflict of interest

The authors state that there was no conflict of interest.

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