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Effects of oxcarbazepine versus carbamazepine on tinnitus: A randomized double-blind placebo-controlled clinical trial

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Hooshang Gerami[1], Alia Saberi[2], Shadman Nemati[1], Ehsan Kazemnejad[3], Mohammad Aghajanpour[4]

[1] Associate Professor, Department of Otolaryngology Head and Neck Surgery, Guilan University of Medical Sciences, Rasht, Iran
[2] Assistant Professor, Department of Neurology, Guilan University of Medical Sciences, Rasht, Iran
[3] Assistant Professor, Department of Biostatistics, School of Nursery and Midwifery, Guilan University of Medical Sciences, Rasht, Iran
[4] Resident, Department of Otolaryngology Head and Neck Surgery, Guilan University of Medical Sciences, Rasht, Iran

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Tinnitus, Anticonvulsants, Carbamazepine, Oxcarbazepine

Abstract

Background: It is still a challenge to find an effective treatment for tinnitus. The aim of this study was the evaluation of carbamazepine and oxcarbazepine effects on tinnitus.

Methods: In a randomized double–blind clinical trial, 57 patients who were visited in a university hospital due to chronic non-pulsatile tinnitus, were randomized in three groups and treated with carbamazepine (300-600 mg/day), oxcarbazepine (450-900 mg/day) and placebo for 12 weeks. Visual analogue scale (VAS) and tinnitus severity index (TSI) were measured in all subjects in the beginning and at the end of the 8th and 12th weeks of the trial. Data was analyzed by repeated measure analysis, paired and independent t-test.

Results: Among 51 participants who completed the trial course (28 men, 23 women), carbamazepine, oxcarbazepine and placebo decreased tinnitus severity in 56.6%, 46.2% and 38.5% of patients according to VAS, and in 61.1%, 58.8% and 50% of patients according to TSI, respectively. The effects of carbamazepine and oxcarbazepine were better in the first 8 weeks of treatment. However, their effect on tinnitus did not show any statistical difference in comparison with placebo (P = 0.34, P = 0.28).

Conclusion: Carbamazepine and oxcarbazepine are not more effective than placebo in decreasing tinnitus severity.

Introduction

Tinnitus is the perception of noise in the absence of corresponding external acoustic stimulation.[1] The prevalence of persistent tinnitus is estimated to be 6 to 30% of general population, and 1 to 3% in adult population. It is absolutely a disabling symptom which could impair quality of life significantly.[2,3] It can be resulted from a wide spectrum of underlying central and peripheral etiologies, and various kinds of medications have been claimed to suppress tinnitus with varying degrees of clinical reliability.[4] Despite considerable research efforts, there is no generally accepted effective treatment for tinnitus and the efficacy of most interventions for tinnitus therapy have remained to be demonstrated conclusively.[5]

One of the possible mechanisms of tinnitus is nerve irritation and seizure type activities in cortical and subcortical areas of the brain, and perhaps this may be the reason that such patients would be likely to respond to anticonvulsants.[6,7]

Email: ijnl@tums.ac.ir

Corresponding Author: Alia Saberi, MD
Email: aliasaberi@yahoo.com

Several trials have investigated the effectiveness of anticonvulsants (such as carbamazepine, gabapentin, etc.) on the subjective idiopathic tinnitus. However, recent meta-analyses showed a small favorable effects, and additional studies on the doses and duration of treatment with anticonvulsant, either alone or as adjunctive therapy in specified populations are needed.[5,8-14] Our survey was carried out to compare the efficacy of two anticonvulsants, carbamazepine and oxcarbazepine (an analogue of carbamazepine with fewer adverse effects and drug interactions), and placebo in treatment of tinnitus.

Materials and Methods

A blocked randomized double-blind clinical trial was conducted in a university referral hospital in Guilan in the north of Iran from April 2010 to May 2011. The proposal of the research was reviewed by Otolaryngology–Head and Neck surgery Research Center and approved by Ethics Committee of Research Office of Guilan University of Medical Sciences.

Participants were recruited from all referred patients with the complaint of tinnitus after explaining research processes for them and obtaining written informed consent. After taking a thorough medical history and performing a complete ear-nose-throat physical examination, a total of 57 patients with persistent non-pulsatile tinnitus lasting for at least 6 months and without any positive history of thyroid disorders, rheumatologic disorders, acute and chronic otitis media, and exposure to excessive or loud noise were enrolled in the study. All of the patients who had unilateral tinnitus and/or sensory-neural hearing loss and/or signs or symptoms of central nervous system involvement underwent brain magnetic resonance imaging (MRI).

Audiometric evaluation and laboratory tests (liver function tests, fasting blood sugar, complete blood count, blood urea nitrogen, blood creatinine, and serum sodium level) were performed before enrollment and were repeated 3 weeks after initiating the medications. The patients were notified to refer to the hospital as soon as possible if encountering fever, sore throat, skin rash, unusual bleeding or bruisability during trial course.

Patients were allocated to three groups using random blocks and received carbamazepine, oxcarbazepine, and placebo in each group using a double blind manner. Considering the confidence coefficient of 95%, study power of 80% and calculation of 10% drop out, the sample size was estimated to be 19 subjects in each study group.

The patients in the first group were prescribed a course of carbamazepine 300 mg/day (before sleep time) for one week, followed by 600 mg/day till 12th week. Treatment in the second group was initiated with 450 mg/day oxcarbazepine for one week, followed by 900 mg/day till 12th week. The placebos were individually enclosed in the same shape tablets and were given in the same manner. In all three groups at the end of the treatment, drugs were tapered during a 2 weeks course.

Before initiating the treatments, the severity of tinnitus and its impacts on quality of life were evaluated by visual analogue scale (VAS) and tinnitus severity index (TSI) and these were repeated at the end of the 8th and 12th weeks of study. By VAS, the patients determined the grade of their subjective perception from severity of tinnitus on a scaled bar in which number one introduced none or minimally severe tinnitus and number 10 maximum imaginable severity of tinnitus.

TSI was calculated according to a 12-item questionnaire about tinnitus impacts on patients' concentration, sleep and quality of life. Each item was scaled from 1 (never) to 3 to 5 (always or to a great deal of discomfort) with maximum total score of 56.[8] At the end the study, data was analyzed by repeated measure analysis, paired and independent t-test in SPSS 18 software (SPSS, Inc., Chicago, IL, USA). Level of statistical significance was considered as $P < 0.05$.

Results

Among 57 participants in our trial, 6 patients dropped out from the study. Two patients abandoned the treatment because of skin allergic reactions, one to carbamazepine and another one to oxcarbazepine, and 4 patients refused completion of treatment course (one from the carbamazepine group, one from the oxcarbazepine group and two patients from the placebo group). No any other side effect was seen during trial course, and no significant change in serum sodium level and liver function profile was seen in the initial 3-week course of treatment with carbamazepine or oxcarbazepine.

From 51 participants who completed the trial course (28 men and 23 women) with mean age of 51.9 ± 10.2 years, 18 subjects were in the carbamazepine group, 17 in the oxcarbazepine group and 16 in the placebo group. Nineteen cases had bilateral tinnitus, while 17 and 15 cases had unilateral tinnitus with more severity in right and left sides, respectively. Our patients mostly suffered from whistling, chirp or continuous roaring tinnitus subtypes and none of the patients suffered from a tinnitus with a staccato quality similar to a type-writer tapping, popcorn popping or Morse code signal. The study groups were adjusted for age, sex, and tinnitus quality and severity during analysis. None of the cases had conductive hearing loss, and

the mean (±SD) hearing level (according to pure tone audiometric thresholds in 250 Hertz to 8 kilohertz) was calculated as 24.9 ± 11.7 dB.

At the end of the treatment and based on VAS, carbamazepine, oxcarbazepine and placebo decreased tinnitus severity in 62.5%, 61.5%, and 38.5% of the cases, respectively. However, compared to the state before treatment, only carbamazepine significantly affected on tinnitus severity at the 8th and 12th weeks of trial (P = 0.006), in contrary to oxcarbazepine and placebo. The mean of decrement with carbamazepine according to VAS score was 1.7 units (95% CI: 0.44-2.17) (Figure 1).

According to TSI, the decrement of tinnitus severity in mentioned groups was observed in 94.5%, 82.4%, and 75% of subjects, respectively. In this regard, both carbamazepine and oxcarbazepine significantly reduced tinnitus severity after 8th and 12th weeks of the trial (P < 0.0001 and P = 0.008 respectively). This effect was not significant in the placebo group at the end of 8th week (P = 0.157), but it was statistically significant at the 12th week (P = 0.033) (Figure 2). The changes of TSI by carbamazepine and oxcarbazepine in comparison with placebo in different periods of treatment are shown in table 1.

According to both scales (i.e. VAS and TSI), there was not any significant statistical differences between carbamazepine, oxcarbazepine and placebo, in reducing tinnitus severity. It was noticed that the effects of both drugs on reducing tinnitus severity were mainly seen in the first 8 weeks of treatment, in contrary to placebo that its effect was steady before and after the 8th week.

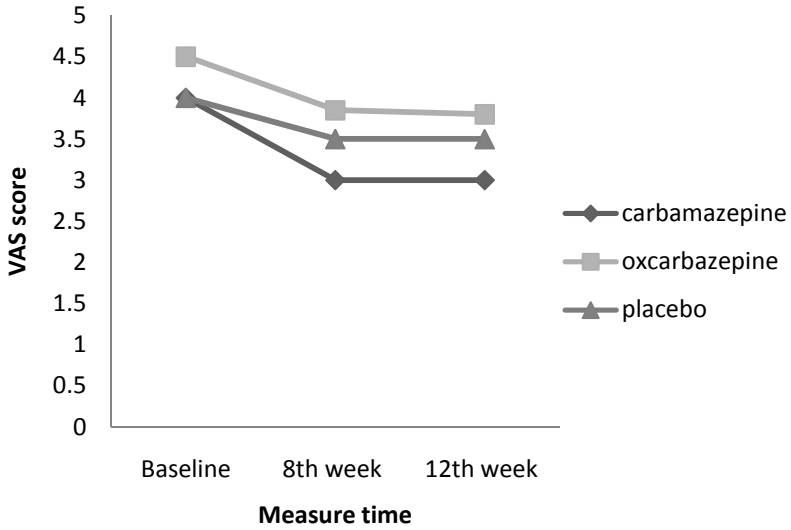

Figure 1. The mean of visual analogue score (VAS) of tinnitus severity at the baseline and at the end of 8th and 12th weeks of trial

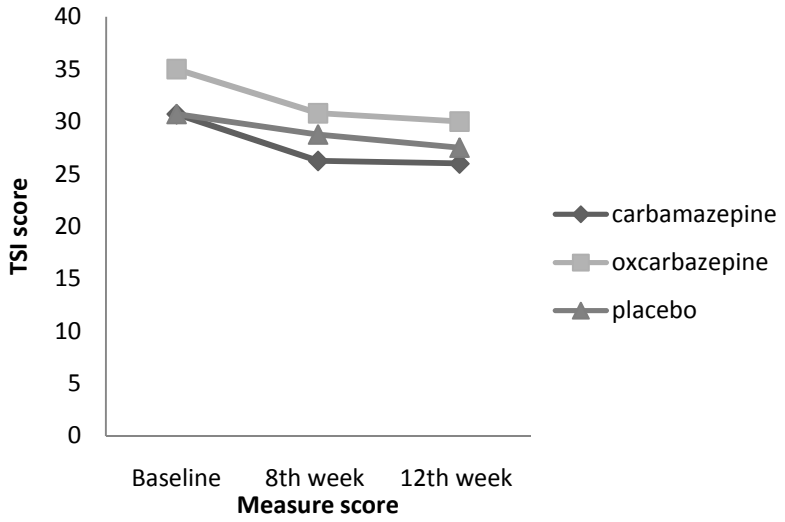

Figure 2. The mean of Tinnitus Severity Index (TSI) at the baseline and at the end of 8th and 12th weeks of trial

Table 1. The change of tinnitus severity index by carbamazepine and oxcarbazepine in comparison with placebo in the measurement periods of study

Period of times	Group	TSI change (Mean ± SD)	P
before – after 8th week	Carbamazepine	3.9 ± 3.8	0.3
	Oxcarbazepine	4.5 ± 6.2	0.3
	Placebo	2.2 ± 5.9	
before – after 12th week	Carbamazepine	4.5 ± 3.2	0.3
	Oxcarbazepine	5.3 ± 6.0	0.3
	Placebo	3.1 ± 5.3	
between 8th -12th week	Carbamazepine	0.6 ± 2.1	0.6
	Oxcarbazepine	0.8 ± 2.6	0.8
	Placebo	0.9 ± 1.1	

TSI: Tinnitus Severity Index

For comparing and following clinically significant effects of the interventions in our three study groups, considering the cut-off points in both scales (i.e. > 20% decrease in VAS, and > 3 units decrease in TSI), carbamazepine decreased tinnitus severity in 56.2% and 61.1% of participants (P = 0.003, P < 0.0001); and oxcarbazepine suppressed tinnitus severity in 46.2% and 58.8% of the participants according to VAS and TSI, respectively (P = 0.06, P = 0.002). But in the placebo group, tinnitus severity was reduced in 38.5% and 50% of subjects, respectively, that the latter was marginally significant (P = 0.33, P = 0.05) (Tables 2 and 3).

Discussion

For the first time in the present study, oxcarbazepine (a new analogue of carbamazepine with fewer side effects and drug interactions) was used for decreasing the severity of tinnitus in comparison with carbamazepine and placebo. We also used TSI in addition to VAS that was used in other studies such as Shiley et al.[8] and Sanchez et al.[15] studies, to consider the effects of interventions on the patients' quality of life.

In our study, among those participants who treated with carbamazepine, 56.2% obtained more than 20% relief of tinnitus severity according to VAS, but 46.2% of participants who received oxcarbazepine and only 38.5% of those in placebo group obtained more than 20% relief of tinnitus severity according to the same score without statistically significant association. Considering more than 3 units reduction in TSI scale, carbamazepine and oxcarbazepine significantly reduced tinnitus severity in 61.1% and 58.8% of participants, respectively. Moreover, placebo significantly suppressed tinnitus severity in 50% of participants. Although carbamazepine and oxcarbazepine did not have any statistical superiority over each other in suppressing tinnitus severity, it seems that carbamazepine is clinically more effective than oxcarbazine and especially than placebo.

In Sanchez et al. study,[15] tinnitus intensity was suppressed in 50% of participants with carbamazepine, but the amount of reduction was not mentioned. In Mardini's study, participants suffering from typewriter tinnitus had an outstanding response to carbamazepine therapy.[16] In Kong et al. trial, efficacy of carbamazepine combined with flunarizine for treating tinnitus did not have any superiority to the control group who were managed by a combination of flunarizine and vitamin B6.[17] In

Table 2. Percent of patients with different reduction of tinnitus severity according to visual analogue scale during 12 weeks of therapy

Group	VAS reduction < 20%	VAS reduction = 20-50%	VAS reduction = 50-80%
Carbamazepine (%)	43.8	43.8	12.5
Oxcarbazepine (%)	53.8	38.5	7.7
Placebo (%)	61.5	30.8	7.7
Total (%)	52.4	38.1	9.5

VAS: Visual Analogue Scale

Table 3. Percent of patients with different reduction of tinnitus severity according to tinnitus severity index during 12 weeks of therapy

Group	TSI reduction ≤ 3 unit n (%)	TSI reduction > 3 unit n (%)	Total
Carbamazepine	7(38.9)	11(61.1)	18(100)
Oxcarbazepine	7(41.2)	10(58.8)	17(100)
Placebo	8(50.0)	8(50.0)	16(100)
Total	22	29	51

TSI: Tinnitus Severity Index

Witsell et al. trial, the difference of tinnitus loudness improvement rate between the experimental group (managed by gabapentin) and control group was not statistically significant.[18] In another study, 1800–2400 mg/day of gabapentin showed a paramount efficacy in controlling tinnitus after acoustic trauma.[19]

In our study, the reduction of tinnitus severity in carbamazepine and oxcarbazepine groups during the first eight weeks of treatment was significantly more prominent compared with the period of time between the 8th and 12th week. This may be due to psychodynamics of tinnitus per se, or may be due to pharmacodynamic characteristics of the drugs. On the other hand, in order to achieve better results, perhaps we should increase the drug dosage after 8 weeks of treatment.

Tinnitus is a vague topic in otology and neurotology with many unsolved questions around it. One of these ambiguities is a large placebo effect that we observed in the treatment course of these patients, a phenomenon that is observed in many other clinical situations, especially in analgesia. Obviously, placebo factors have neurobiological underpinnings and actual effects on the brain and body, and the demonstration of the involvement of placebo mechanisms in clinical trials and routine clinical practice have interesting considerations for clinicians and researchers.[20]

For achieving better results, we suggest doing the study with more participants in each group and also with incremental dosages of carbamazepine and oxcarbazepine after 8 weeks. Dividing tinnitus according to accompanying disorders (psychological disorders, presbycusis, acoustic trauma, underlying medical diseases) also can help in finding better strategies in tinnitus treatment.

Conclusion

Carbamazepine and oxcarbazepine are not significantly more effective than placebo in decreasing tinnitus severity. However, carbamazepin and oxcarbazepine are clinically effective in this regard.

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