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THE COMPARATIVE STUDY OF TWO DRUGS OF CARBAMAZEPINE AND BETAHISTINE ON TINNITUS IMPROVEMENT

Leila Mashali¹, Somayeh Rahimi^{2*}, Hosein Rekabi¹, Parisa Rahimi³

¹Associate professor, department of ENT, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

² Student Research Committee, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

³ Doctor of medicine, Islamic Azad University of Medical Sciences, Tehran, Iran

Email: somayehrahimi12@gmail.com

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Abstract

Background and Objective: Tinnitus is a common complaint among patients who refer with ear problem; according to multiple etiologies of tinnitus and lack of understanding of its indication mechanism, finding an effective treatment method is still a challenge. The purpose of this study was the study of carbamazepine and betahistine effect on tinnitus of referred patients to Ahvaz Imam Hospital.

Materials and Methods: This was a clinical trial conducted on patients (23 to 65 years old) with non-pulsatile tinnitus from May 20015 to 2016 in Ahvaz Imam Hospital. A total of 73 patients were randomly divided into three groups: Two intervention groups received carbamazepine (200-400) and betahistine (16mg), and one placebo group who received placebo drug for 12 weeks. The measures were audiometric tests and Tinnitus Severity Index (TSI) that were performed pre- and post-intervention. Data were analyzed with SPSS statistical package.

Results: Of the 73 patients, carbamazepine was superior to placebo and betahistine ($P= 0.007$), but Betahistine was not superior to placebo.

Conclusion: Carbamazepine and betahistine drugs are effective in decreasing the patients' tinnitus intensity, whereas betahistine is not significantly more effective than placebo.

Keywords: Tinnitus, Anticonvulsants, Carbamazepine, Betahistine.

Introduction

According to a theory, the word of Tinnitus from Latin word of Tinnire means «To ring» (1). Treatment history of it goes back to ancient Egypt (2). Tinnitus creates as feeling a noise or ring in one or both ears or inside the human head in the absence of external auditory stimulus (3) (4). Tinnitus is divided into two kinds of subjective and objective

tinnitus. In type of objective, except patient, the examiner also hears the tinnitus but in type of objective, tinnitus has been heard only by patient. Tinnitus prevalence in the general population is about 17% (5-8).

Epidemiological studies have shown that tinnitus is a very common phenomenon that people of all ages will experience it (9-12). Permanent tinnitus and galling is observed in 6-30% of community members and in 25% of these individuals (About 4% of the population) is so severe that is affected on their quality of life (13, 14). It causes insomnia, disorder in concentration, Job and mental health problems and has heavy social and economic burden (15).

Based on a theory which assumes the tinnitus as a type of seizure activity (seizure type) in cortical and sub-cortical areas of the brain that leads to perceive an impaired or improper hearing, the use of antiepileptic drugs was common for reduction of patients' tinnitus (16-19). In this double-blind and placebo-controlled study, the effects of carbamazepine and betahistine have been investigated. These two drugs are analogue of histamine with fewer potential complications for reduction or emancipation of patients from annoying tinnitus of patients.

Materials and Methods

Proposal of research was approved in Ear Nose Throat Research Center of Medical Sciences University of Ahvaz and was confirmed in research assistance of University Ethics Committee. This clinical trial was conducted from August 2015-2016 in Imam Khomeini hospital of Ahvaz. The study was done on patients 21 to 65 years with chronic tinnitus. Inclusion criteria of patients include: 1- Experience tinnitus for more than 6 months 2- The presence of non-pulsatile tinnitus among the individuals aged 21 to 65 years old. Exclusion criteria of patients include: 1- The presence of pulsating tinnitus 2- The presence of meniere's disease 3- Neuroma and vestibular 4- Otosclerosis 5- Patients who use a hearing aid 6- Gestation 7- Mental illness that has been required to treatment 8- In case of intolerance of the dose minimum of medications (carbamazepine) or history of hypersensitivity to mentioned drugs 9- Treatment with antiepileptic drugs 10- OCP consumers and the drugs that with carbamazepine have drug Interference and their use is mandatory for patients. 11- Patients with severe heart disease 12- (IHD-CHF the incidence of drug allergies with severe drug reactions during treatment. The referred patients initially were full evaluated by an ear, throat and nose specialist to any underlying disease associated with tinnitus be identified and discarded. This examination included a detailed clinical examination, examination of the external ear and tympanic, temporomandibular joint assessment and cranial nerve examination. Before treatment, required laboratory tests (CBC), LFT= Liver function tests, Na= sodium, FBS, Cr, Bun was requested for patients. Then for above patients were done audiometry tests. Audiometry tests include tympanometry, SDS, ART, PTA. Then, tinnitus Severity

index questionnaire were completed for patients. Moreover, there are other questionnaires to assess the severity of tinnitus. Despite all these questionnaires, the tinnitus severity index (TSI) enjoys its brevity and in terms of application and scoring is easier. 2) Various stages of clinical trial were described for patients and after obtaining written consent were divided into three categories and were randomly placed in three groups in terms of sex, age, and tinnitus severity. A category carbamazepine (A), a category betahistine (B), and a placebo (C) were received. Patients with mentioned treatment were treated for 12 weeks; Treatment was began with low doses and reached to the main dose within two weeks (Which of course it is low dose than neurological treatment). All patients at the beginning of treatment and third week after the start of treatment with necessary tests were evaluated and studied in potential complications prescribed drugs which if creation of potential complications that do not be able to continue the research project, be excluded from the study.

Patients were also informed, in case of fever, sore throat, skin rash, unusual bruising and bleeding, immediately visit a doctor of plan in the hospital. Category of carbamazepine (A): During the first week of start with 200 mg in night and then, in second week was rose to dose 200 mg twice a day and by the end of the period of 12 weeks was continued with 400 mg per day. Data were recorded according to patients' response to the TSI questionnaire and audiometry tests (severity of tinnitus); also demographic information and initial examination of patients were registered in the questionnaire that is attachment. Category of betahistine (B), two tablets 8mg daily were given to referred patients for three months; category (C) of control group was prescribed drug with the way of same consumption with previous groups. After the week 12, the patients were treated as Tapering within 2 weeks and TSI questionnaire was completed for all participated patients in the plan. (TSI) questionnaire includes 12 questions about the effects of tinnitus on focus, sleep and daily activities of patients that any questions have from 3 to 5 points (From one equivalent of never, to five equivalent of always) and maximum 56 points can belong to it. For data analysis was used to compare the tinnitus severity based on TSI before and after the consumption of drugs to separation of measured times from chi-square and unilateral variance analysis and separation test of LSD and then, results obtained were analyzed using SPSS16 software.

Results

From 3 people of participant in the project, 24 people were placed in the carbamazepine group and 25 patients in betahistine group and 24 patients in the placebo group, which to compare sex and age distribution in three investigated groups was used from chi-square test that as a result, it was $P=0/99$ and was not observed a significant

difference and three groups were same in term of sex and age. In each treatment group of carbamazepine and betahistine was not observed a change in profile of blood sodium serum and liver function tests in the third week after treatment to before treatment. The average TSI scores in the three groups were respectively 26.41 ± 7.05 , 32.54 ± 7.7 , and 32.52 ± 8.08 . The pre and post intervention mean scores of TSI showed a significant difference. The one-way analysis of variance was used for comparison of averaged changes in three groups (Table 1).

Table-1. Demographic data of the three groups of the study.

group	Mean	N	Std. Deviation
Carbamazepine	3.04	24	2.49
Betahistine	1.70	24	1.73
Placebo	1.6800	25	2.09603
Total	2.1370	73	2.19415

For groups that differed their mean was used from LSD test which there was a significant difference between the receiving group of carbamazepine compared with receiving group of betahistine and placebo with $p_{\text{valu}}=0/007$. But there was not a significant difference between the receiving group of betahistine and placebo with $p_{\text{valu}}=0/99$.

Discussion

In many studies, antiepileptic drugs has been considered such as carbamazepine and gabapentin for reduction of tinnitus which is in the most recent conducted meta-analysis and systemic reviews has a significant impact, especially against the not seen possible complications and risks and also implementation of more studies and with higher quality need in this survey and using new drugs less lateral complications. In this study, the effect of betahistine less lateral complications has been considered in reduction of tinnitus to carbamazepine or placebo. In this study, patients with non-pulsatile tinnitus for 12 weeks at two different times of before and after 12 weeks were investigated with TSI test. In this study, carbamazepine was significantly decreased the tinnitus severity based on TSI with $p=0/007$ which the effect of this case in reduction of tinnitus was significant in term of statistics. Also, there was a significant differences between the receiving group of carbamazepine compared with receiving group of betahistine and placebo with $P=0.007$ but there was not a significant differences in receiving group of betahistine and placebo with $P=0.99$. Gerami et al. study that was conducted in 2012 showed that from of 57 patients (23 to 65 years) with non-pulsatile tinnitus, with carbamazepine (mg 300-600), versus oxcarbazepine (900-450mg) and placebo were cured for 12 weeks

in three separate groups, in the beginning of the study were acquired the physical examination and laboratory tests, audiometry test and complete the test TSI (Tinnitus Severity Index) then, VAS and TSI questionnaires was completed for patients at the end of week 8 and 12. Of 51 patients that completed the treatment period (28 males and 23 females), carbamazepine versus oxcarbazepine and placebo decreased tinnitus severity based on VAS respectively 56.2%, 46.2% and 38.5 of patients. Reduction of tinnitus severity based on TSI in the three mentioned groups was respectively 61.1% and 58.8%, and 50%. In the comparison between studied groups, carbamazepine and oxcarbazepine had not superiority to placebo in reduction of patients' tinnitus based on VAS and TSI (20).

Donaldson (1981) showed that treatment with carbamazepine 200 mg twice a day for 2 months has had the positive effect to rate of 45% reduction, in tinnitus compared with 21% in the placebo group. In 1998, Hulshof showed that treatment with carbamazepine 150 mg in three times a day for one month had not a positive effect in the treatment, so that 8% vs. 13% have been the result of this study at the placebo group (21). That less time was used in this study but in present study the dose rate of drug was increased to 400mg until the end of week 12. That compared with studied groups, carbamazepine had superiority to betahistine and placebo group with $p = 0/007$ which in term of statistics was significant (21). In a study by Genece et al. (2011) in Brazil, they showed that 35% (80.262) of patients who have been treated with betahistine, improved their tinnitus and compared with control group 17.1 (33/252), the results showed that betahistine with $P < 0.0001$ with 8 mg dose daily for 120 consecutive days has been remarkable in improvement patients' tinnitus. As a result, betahistine have been useful in reduction or removal of patients' tinnitus with vestibular diseases (22). In present study, betahistine had not superiority to the placebo group and statistically was not significant with $p = 0/99$. In a study that was conducted in 2010 by Elgoyhen et al. in Argentina, recovery percent of patients' tinnitus with carbamazepine have been salient (19). In a study in 2009 conducted Salvia et al. in America showed that, carbamazepine has had a significant recovery in the number of patients who with tinnitus (23). In a study in 2009 that was performed by Julianne savage et al. on 48 patients with tinnitus for 30 days. In a group of 24 persons received carbamazepine with dose of 150 mg three times a day that result was 2/24 (8%) that compared with placebo group 3/24 (13%), the recovery rate has not been impressive with carbamazepine (24). In a study in 2008 that was conducted by zheng et al. in New Zealand, carbamazepine effect on tinnitus was investigated, in this study by salicylate injection created the tinnitus in Rat and then the effects of carbamazepine in the treatment and reduction of tinnitus were studied in the mice; results showed that consumption of 15 ml/kg of carbamazepine in mice has had significant impact in decrease of tinnitus in these (25). A study by Tanit et al. (1999), the drug of local

anesthetic lidocaine effects on the membrane of cochlear hair cells and nerve fibers; IV lidocaine effect is transient

but many oral anticonvulsant drugs such as carbamazepine were investigated in many studies. In this study, 50 patients were evaluated who had consisted of 28 women and 23 men with age mean of 50.9 that lidocaine and carbamazepine effect were examined in reduction of tinnitus on them. Lidocaine chloride 2% for injection was used within 2 minutes and oral carbamazepine for increasing dose was given to them from 50 to 600 mg per day, the results showed that 18% of patients was resolved their tinnitus, 32% have greatly diminished, 26% low, 32% not changed and 2% of patients got worse. In total, 50% of those who received carbamazepine, their tinnitus were better $P = 0.0034$ and 76% lidocaine was effective in reduction of patients' tinnitus especially in people who have had bilateral tinnitus $P < 0.001$. The result showed that IV lidocaine and carbamazepine have had a similar effect in decrease of tinnitus, so carbamazepine can be used in improvement of tinnitus of individuals who would improve their tinnitus after lidocaine test for long-acting (26).

In a study by Alex et al (2013), the effect of piracetam and carbamazepine was compared in treatment of tinnitus; piracetam with $p < 0.001$ had significant reduction in decrease of patients' tinnitus compared with carbamazepine; carbamazepine also caused the patients' tinnitus, but its effect was not significant (27).

Conclusion

Our findings showed that carbamazepine drug compared with betahistine and placebo drugs had a significant impact in reducing tinnitus of patients but betahistine have not had superiority to placebo. It is recommended to get a better result, first: The mentioned study be done in wider level with number of more participants in each group and with increasing dose of carbamazepine and betahistine drugs, second: Classification of tinnitus based on its associated diseases such as mental disorders, presbycusis, damage caused by acoustic trauma and underlying medical and the study of drugs impact in these subgroups can be considered more precise strategies for evaluating a therapeutic method, including drug or non-drug methods. In addition, it seems that finding of new approaches of tinnitus control in the future required research and promotion of medical treatments of Neuroscience and effective of course is dependent to understand the changes of neurotransmitters and their receptors and until these mechanisms are not well understood in how of perception of tinnitus, designing of a precise therapeutic method will fail.

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Corresponding Author:

Somayeh Rahimi*,

Email: somayehrahimi12@gmail.com