

Comparison of Melatonin and Sertraline Therapies on Tinnitus: A Randomized Clinical Trial

Abstract

Background: Tinnitus is the perception of noise or ringing without external acoustic stimulants which affects almost 10% of general population. Many therapies have been recommended including diet modifications, herbal remedies, and chemical drugs. Most common utilized drugs for tinnitus are melatonin and antidepressants such as sertraline which have been proven in different studies. In this study, we aimed to compare the efficacy of melatonin and sertraline in treating tinnitus for the first time. **Methods:** In this clinical trial, 70 patients with tinnitus according to inclusion and exclusion criteria were included and randomly divided into two groups: melatonin group, taking melatonin 3 mg once daily and sertraline group taking sertraline 50 mg once daily, all treating for 3 months. Before and after treatments, every patient received Tinnitus Handicap Inventory (THI) questionnaire and severity of tinnitus was assessed, and data analysis was performed. **Results:** Before treatments, the mean of THI score for melatonin and sertraline groups were 45.02 ± 17.67 and 44.85 ± 20.57 , respectively. There was no significant difference between both groups THI score ($P = 0.23$). After 3 months, the mean of THI scores for melatonin and sertraline groups were 30.29 ± 19.62 and 36.96 ± 25.03 , respectively which the mean of THI scores in two groups was decreased significantly ($P < 0.01$, for-both). In addition, indicated the significant decline in THI score of melatonin group who were under treatments with melatonin 3 mg once daily ($P = 0.02$). **Conclusions:** Here in this clinical trial, we demonstrated that both melatonin and sertraline are efficient in treating tinnitus, but the usage of melatonin 3 mg once daily is more effective.

Keywords: Melatonin, sertraline, tinnitus

Introduction

Tinnitus is described as a perception of ringing or noise with the absence of external acoustic stimulant. Tinnitus can cause problems which include but is not limited to, sleep loss, and concentration difficulties for patients which can be developed in one or both ears and it can also affect normal people or even deaf population.^[1] Epidemiologic studies revealed that almost 50 million of United States peoples suffer from Tinnitus and as Hoffman reports, the prevalence of Tinnitus is about 10%–15% in adult population.^[2] Tinnitus is divided into two main categories: subjective and objective. The objective form is a rare form of tinnitus which includes <1% of all cases. On the other hand, subjective form of tinnitus is most prevalent and is classified into conductive, sensorineural, and central.^[3] Although there is much

uncertainty of the exact mechanism of tinnitus, several hypothesis exist and the most common of all is prolonged exposure to a loud noise.^[4] As Herraiz *et al.*^[5] claims, the neurophysiology of autonomous nervous response to tinnitus, which contains anxiety, depression, and sleep disorders, is because of the connection between the limbic system and auditory pathways. As mentioned above, the most important difficulty, associated with tinnitus is sleep disturbance which is demonstrated to have highly correlated to tinnitus severity.^[6] Albeit there have been several different therapies for tinnitus such as diet modification, habits treatments, and herbal remedies, but none of these treatments had been proved to be a specific treatment of tinnitus. There have been also some researches about the impact of melatonin in tinnitus treatment along with its established role in sleep disorders and the role of melatonin in sleep-awaking cycles and some report that patients have

Seyed Hamidreza Abtahi,
Seyed Mostafa Hashemi,
Mahdi Mahmoodi,
Mohammad Hossein Nilforoush¹

Department of Otorhinolaryngology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran, ¹Audiology Department, Communication Disorders Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

Address for correspondence:

Dr. Mahdi Mahmoodi,
Department of Otorhinolaryngology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: Dr.mahdi.mahmoodi@gmail.com

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had benefits from treatment with melatonin.^[4,7] On the other hand, there are much mentions about the relation of psychotic disorders and tinnitus and some studies had been investigating the role of antidepressant therapies in tinnitus.^[8,9] One of the important drugs, selective serotonin reuptake inhibitors (SSRIs) can truly affect both depression and anxiety disorders and are well proven to be safer than tricyclic antidepressants.^[10] In this study, we aimed to investigate and compare the effects of melatonin and sertraline (a member of SSRI group) in treating tinnitus.

Methods

In this clinical trial double-blinded; that approved in vice chancellor for Research, Isfahan University of Medical Sciences and registered in Iranian Registry of Clinical Trial (No: IRCT2017011412782N13), 98 patients with chief complain of tinnitus which were referred to Al-Zahra and Kashani Hospital in Isfahan-Iran from 2015 to 2017 were admitted. 70 patients were volunteered to take part in our study according to inclusion and exclusion criteria. All patients, (28 males and 42 females), diagnosed with tinnitus by expert otolaryngologist, were included and randomly divided into two groups: melatonin group (16 males and 19 females), taking melatonin 3 mg once daily and sertraline group (12 males and 23 females) taking sertraline 50 mg once daily, all treating for 3 months, also patients were blinded to treatment types (melatonin or sertraline therapy). Our inclusion criteria were included: having tinnitus for at least 6 months, normal audiogram test, having no drug allergy to sertraline, melatonin, and benzodiazepine drug family. Also patients who have tinnitus due to specific ear issues such as Meniere's disease, otitis, labyrinthitis, ear wax, Eustachian tube obstruction, recent taking of drugs which commonly cause tinnitus, recent history of the trauma such as acute or chronic acoustic trauma, and evidence of audiogram test indicating neurological conduction problems were not meeting inclusion criteria. In addition, exclusion criteria were included noting follow up until 3 months and having severe side effects with medicine consumption. Before treatments, patients in both groups received Tinnitus Handicap Inventory (THI) questionnaire that includes 25 questions and scored between 0 to 100 for assessing tinnitus severity, this questionnaire measured level of tinnitus with questions that have effect on the quality of life, and also THI questionnaire evaluates effect of tinnitus on sleep, depression, mood, and feels. According to this questionnaire, those patients scoring from 0 to 16 were defined as slight tinnitus or Grade 1, those who scored 18–36 were defined as mild tinnitus or Grade 2, those patients scored from 38 to 56 were defined as moderate or Grade 3, patients who were also scored

58–76 defined as severe or Grade 4 and those patients who were scored 78–100 were defined as catastrophic or Grade 5 tinnitus.^[11] During treatments, one patient from melatonin Group and 2 patients from sertraline group were excluded from this clinical trial [patient's diagram is indicated in Figure 1]. After treatments, all patients received THI questionnaire and were scored again. The relationship between two groups with sex and involved ear was assessed using Chi-square test, independent *t*-test was performed for assessing the relation between groups with age and before and after treatments THI score and also we compared before and after treatment THI score in two groups using Paired-samples *t*-test. All data were analyzed using SPSS software version 22 (International Business Machines Corp. New Orchard Road Armonk, New York, USA) and shown as number (percent) and mean \pm standard deviation. Furthermore, $P < 0.05$ was deemed as a statistically significant threshold.

Results

In our clinical trial, 70 patients (42 females and 28 males) with the mean age of 45.17 ± 14.74 years volunteered. All patients were equally randomized into two groups each consisting 35 patients: melatonin group (16 males and 19 females), taking melatonin 3 mg once daily and Group 2 (12 males and 23 females) taking sertraline 50 mg once daily, all treating for 3 months. There were any significant relationship between both groups regarding to age, gender and involved ear ($P = 0.26, 0.32, \text{ and } 0.47$, respectively). In addition, in 47.1% of patients left ear was involved [Table 1]. Before treatments, all patients received THI questionnaire. Before drug treatment, mean of THI score for melatonin and sertraline groups were 45.02 ± 17.67 and 44.85 ± 20.57 , respectively. There was also no significant difference between both groups in THI score ($P = 0.23$). Before any medications, 38.6% of patients had moderate tinnitus according to their score [severity frequencies for before treatment based on THI questionnaire are summarized in Table 2]. After treatments for 3 months, mean THI scores for melatonin and sertraline groups were 30.29 ± 19.62 and 36.96 ± 25.03 , respectively which mean of THI scores decreased significantly in melatonin and sertraline groups ($P < 0.01$, for-both). Also indicated significant decline in THI score in melatonin

Table 1: Demographic information of patients in two groups

Variable	Melatonin group	Sertraline group	<i>P</i>
<i>n</i>	35	35	-
Gender (male/female)	16/19	12/23	0.32
Age (years)	45.68 \pm 15.77	44.65 \pm 13.84	0.26
Involved ear (right/left/bilateral)	10/14/11	7/19/9	0.47

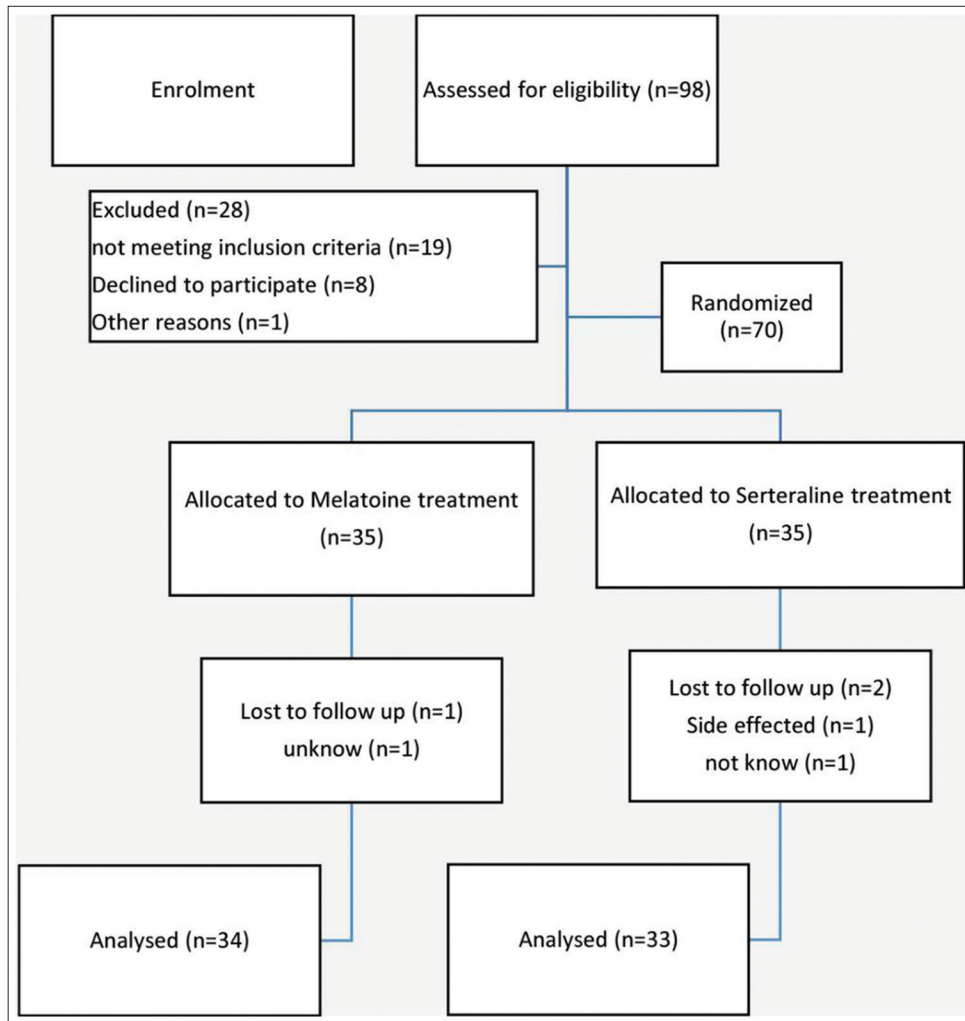


Figure 1: Diagram of the flow of patients through every stage of the study

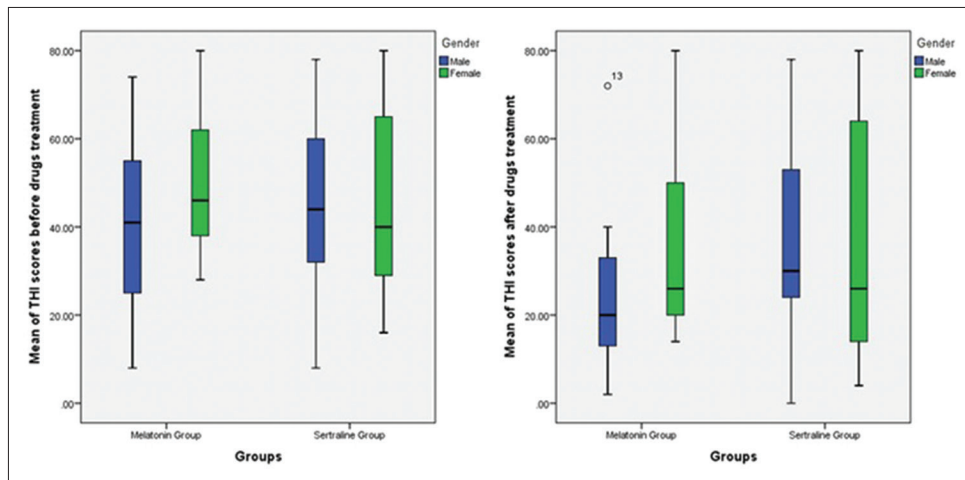


Figure 2: Boxplots of mean of Tinnitus Handicap Inventory scores before and after drugs treatment in groups

group who were under treatments with melatonin 3 mg once daily ($P = 0.02$) [Figure 2]. It should also be noted that after treatments with melatonin, 50% of patients

had mild tinnitus and after treatments with sertraline, 33.3% of patients had mild tinnitus based on their THI score [Table 3].

Table 2: Tinnitus Handicap Inventory Questionnaire information in before drugs treatment

THI questionnaire	Melatonin group (%)	Sertraline group (%)	P
Mean of scores	45.02±17.67	44.85±20.57	0.23
Numbers of severity			
Slight	2 (5.7)	4 (11.4)	
Mild	9 (25.7)	10 (28.6)	
Moderate	16 (45.7)	11 (31.4)	
Severe	7 (20.0)	8 (22.9)	
Catastrophic	1 (2.9)	2 (5.7)	
Total	35 (100)	35 (100)	

THI=Tinnitus Handicap Inventory

Table 3: Tinnitus Handicap Inventory Questionnaire information in after drugs treatment

THI questionnaire	Melatonin group (%)	Sertraline group (%)	P
Mean of scores after drugs treatment	30.29±19.62	36.96±25.03	0.02
Number of severity			
Slight	9 (26.5)	8 (24.2)	
Mild	17 (50.0)	11 (33.3)	
Moderate	3 (8.8)	4 (12.1)	
Severe	4 (11.8)	8 (24.2)	
Catastrophic	1 (2.9)	2 (6.1)	
Total	34 (100)	33 (100)	

THI=Tinnitus Handicap Inventory

Discussion

As mentioned above, melatonin and sertraline are both approved for tinnitus treatments.^[7,10] However, to the best of our knowledge, there has been no comparison between the efficacies of these drugs. Our results revealed that treatments with melatonin 3 mg once daily is more effective for tinnitus treatment than with sertraline 50 mg once daily. Pharmacological studies indicate that melatonin can be also protective against noise- and drug-induced hearing loss.^[12] The protection effects of melatonin against tinnitus have been evaluated in different studies.^[7,13] As Reiter *et al.* have concluded,^[14] melatonin is a safe and cost-effective drug which is effective to decrease drug-mediated ototoxicity by aminoglycosides and cancer chemotherapeutic agents. Along with these findings, it is been also reported that melatonin limits subjective tinnitus in patients by dosage of 3 mg daily. There are also other studies demonstrating that melatonin is helpful and effective for tinnitus therapy.^[7,15] There are some studies that compare the effectiveness of melatonin with melatonin along with other agents. As in a randomized clinical trial by Neri *et al.*,^[3] it was found that however melatonin alone is efficient in treating tinnitus but they also demonstrated melatonin in conjunction with Sulodexide has better effects. In another study by Albu and Chirtes^[16] that intratympanic dexamethasone plus melatonin is more efficient in treating

tinnitus than melatonin alone. Furthermore, there has been also evidence indicating sertraline to be more effective than placebo in treating tinnitus.^[17] Both sertraline and melatonin are widely used by physicians for patients suffering from tinnitus, but in this paper, we showed that melatonin 3 mg once daily has better effects. There are also some conflicting evidences. As Larsen concluded,^[18] both Antidepressants and melatonin have no effects on tinnitus which conflicts with the results of our study and other studies, mentioned above.

Conclusions

Our results demonstrated that both melatonin and sertraline are effective in treating tinnitus and there was a decrease in THI score in both groups but we aimed to compare the results to figure out for the first time that which drug is more efficient. Taken together, we found that melatonin is more helpful than sertraline.

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Conflicts of interest

There are no conflicts of interest.

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