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Comparative Evaluation of Melatonin as an Alternative Therapy in Tinnitus: A Double-Blind, Placebo-Controlled Randomized Trial

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Abstract

Background: Tinnitus is an auditory perception that is described as a perception of noise without any external acoustic stimulant. Tinnitus causes many problems including sleep disturbances and difficulty in concentrating for patients.

Aim: In this trial we evaluated melatonin as an alternative therapy in tinnitus.

Methods: In this clinical trial, tinnitus patients (n = 90) were randomly assigned to 12 weeks of double-blind treatment with melatonin (n = 30) at a fixed-dose (3 mg once daily), sertraline (n = 30) at a fixed dose (50 mg once daily) and placebo (n = 30) once daily. The treatment outcomes were measured using THI (Tinnitus Handicap Inventory), tinnitus loudness score, and tinnitus awareness score after 3 months.

Results: The baseline assessment with THI (Tinnitus Handicap Inventory) showed no significant difference in THI score between groups before treatment (p-value = 0.38). The mean THI score shows a significant decrease in both melatonin and sertraline groups (p-value < 0.03). Overall, a mean of 20% decrease in tinnitus loudness score and a 2-fold decrease in tinnitus awareness score was seen in the melatonin group. In contrast, a mean of 2% decrease in tinnitus loudness score and 25% decrease in tinnitus awareness score was seen in the sertraline group.

Conclusion: Both melatonin and sertraline reduce tinnitus loudness score and tinnitus awareness score within 12 weeks in primary care, but melatonin showed a more significant outcome. Our findings support the prescription of melatonin in tinnitus management.

Conflicts of Interest: The Authors declare no conflicts of interest.
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Introduction

Tinnitus is considered an auditory perception, which is described as a perception of noise without any external acoustic stimulant (1-3). Usually, tinnitus cases are benign and idiopathic. Cognitive behavior therapy is the recommended treatment to improve quality of life in patients with tinnitus (4). The connection between the limbic system and auditory pathways is considered the underlying mechanism of anxiety, depression, and sleep disorders as the autonomous nervous system response to tinnitus (4-6).

There are multiple studies regarding the impact of melatonin on tinnitus patients (8, 9). Besides, selective serotonin reuptake inhibitors (SSRIs) serve as valuable drugs in this field

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(10-12). The actual role of melatonin in comparison with antidepressant in the treatment of tinnitus is less studied.

Methods

Our reporting of this trial was conducted according to The CONSORT statement (10).

This trial was a randomized, double-blind, placebo-controlled study. The study was approved by the local Ethics Committee (IR.SBMU.MSP.REC.1396.80), and randomized clinical trial registry (IRCT2019041804112N1). All participants gave written informed consent.

The study was conducted at the department of otolaryngology and head and neck surgery. In this trial recruitment to the study was based on tinnitus patients who were presented to otolaryngology clinic of our tertiary center. Patients were eligible for inclusion if they had unilateral tinnitus with a normal audiogram in the past one-year. Exclusion criteria were tinnitus due to specific ear disorders (Meniere's disease, otitis, labyrinthitis and drug toxicity), history of recent trauma, comorbid psychosis, schizophrenia, dementia, bipolar disorder, mania, alcohol or substance abuse, medical contraindications for melatonin or sertraline and antidepressant treatment or melatonin usage in the past 8 weeks.

On inclusion, patients were randomly assigned to three groups with a remote computer-generated code using dedicated software (http://www.randomization.com). In each allocation according to recent evidence in optimal dosages patients took one capsule (Melatonin 3 mg, Sertraline 50 mg or placebo) daily for 12 weeks. Researchers and the study statisticians were masked to treatment allocation.

The study allocation were told to physician at the end of the study or when patients withdrew from prescribed medication so they could considered further treatment if needed. Baseline assessments and follow-up assessments at 12 weeks were done in the otolaryngology clinic. To meet blinding, Melatonin 3 mg, Sertraline 50 mg and placebo were encapsulated and packaged in similar boxes.

We assessed tinnitus in the baseline and final assessment with three measurement scales:

1. The tinnitus loudness score (score of 10)
2. The tinnitus awareness score (percentage of time in which the patient is aware of tinnitus)
3. Tinnitus Handicap Inventory (THI).

All participants received the Tinnitus Handicap Inventory (THI) questionnaire (25 – item) that is a self-report scale of the severity of tinnitus based on the quality of life and the effect of tinnitus on patients' sleep, depression, mood, and feels. The available scores ranging from 0–100 and higher scores indicating more severe disease.

According to this questionnaire, THI score 0-16 = slight tinnitus or Grade 1, THI score 18–36 = mild tinnitus or Grade 2, THI score 38 - 56 = moderate or Grade 3, THI score 58-76=severe or Grade 4 and THI score 78-100=catastrophic or Grade 5 tinnitus.

Based on the literature review, meeting the following criteria is considered as a response to treatment: 10% decrease in tinnitus loudness score, a 2-fold decrease in tinnitus awareness score and a 2-fold decrease in THI score (1, 5).

According to non-normal distribution of our data, non-parametric statistics were utilized and data are given as frequencies or median. All data were analyzed using, IBM SPSS statistics for Windows, Version 20.0. A two-sided p-value of ≤ 0.05 was deemed as a statistically significant threshold.

Results

Patients were recruited from July 2018 to December 2019.The CONSORT flow diagram (Figure 1). In this trial, 90 patients (48 females and 42males) with a mean age of 43.12±11.35 enrolled. The youngest participant is 23 years old and the oldest one is 71 years old. All patients were coequally randomized into three groups of thirty: Melatonin group (16 males

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and 14 females), Sertraline group (14 males and 16 females) and placebo group (12 male and 18 female), all conducting for 3 months treatment. Of this 90 patients, 7 withdrew from the study: one due to lost of follow up in Melatonin group, 3 in Sertraline group (2 due to lost of follow up, one due to noncompliance) and 3 in the placebo group, due to noncompliance. Before treatment, the mean of THI score for Melatonin, Sertraline, and placebo groups were 38.75 ± 8.52, 36.91 ± 7.96 and 36.33±6.23, respectively. There was no significant difference between groups THI score before treatment (p-value= 0.38).

After 3 months of treatment, the mean of THI scores for Melatonin, Sertraline and placebo groups were 28.47 ± 7.35, 27.12 ±4.69 and 35.18 ± 11.70, respectively. The mean of THI score showed a meaningful decrease in both Melatonin and Sertraline groups (p-value<0.03) (Figure 2).

In general, a mean of 20% decrease in tinnitus loudness score and a 2-fold decrease in tinnitus awareness score was seen in the melatonin group. In contrast, a mean of 2% decrease in tinnitus loudness score and 25% decrease in tinnitus awareness score was seen in the sertraline group (Figure 3, 4).

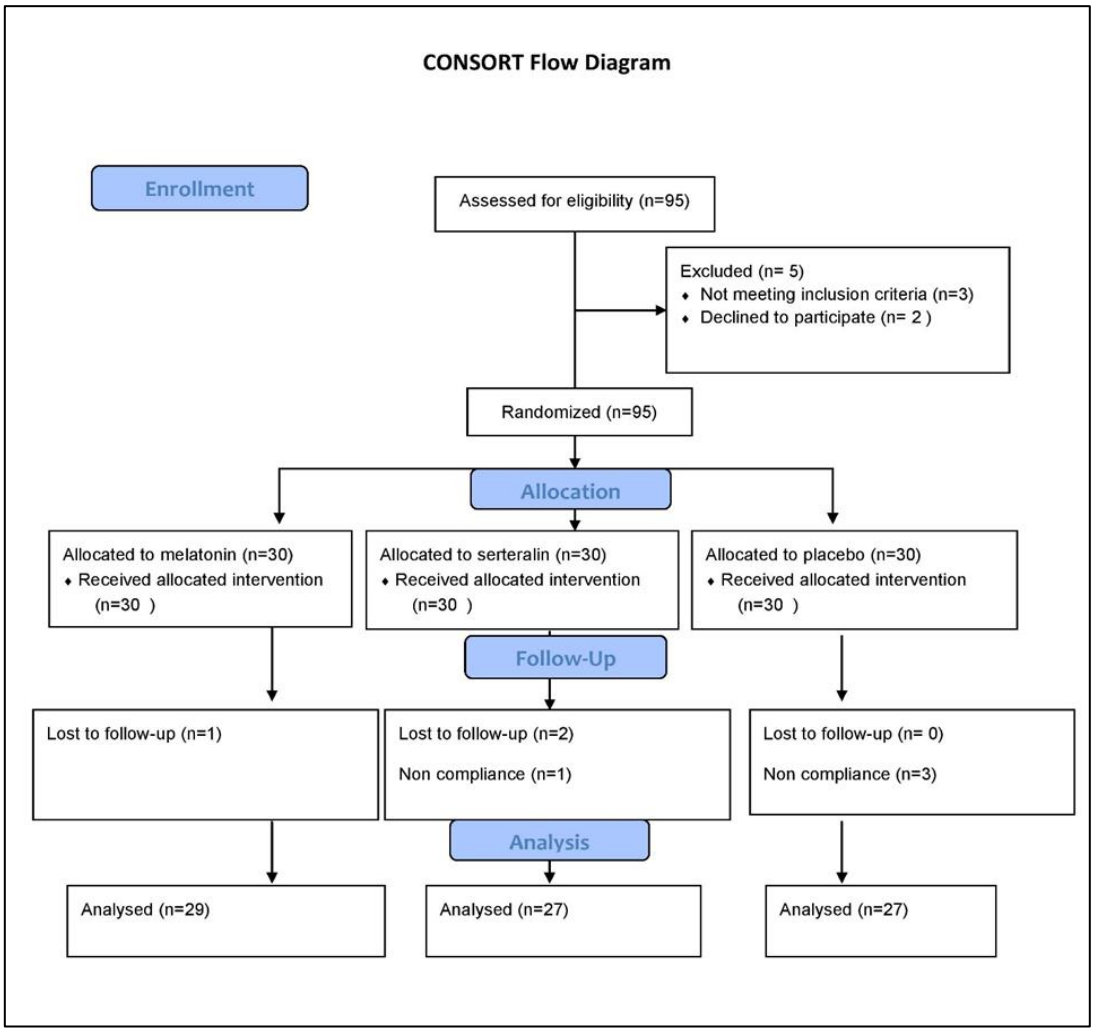

Figure 1. Consort flow diagram show patient allocation, randomization, and follow up showed the participant allocation, follow-up and analysis. Ninety-five patients were assessed for eligibility, 5 were excluded and the remaining 90 were randomized to Melatonin group (n=30), Sertraline group (n=30) and placebo group (n=30). Primary assessment demonstrated that the baseline characteristics were similar between groups.

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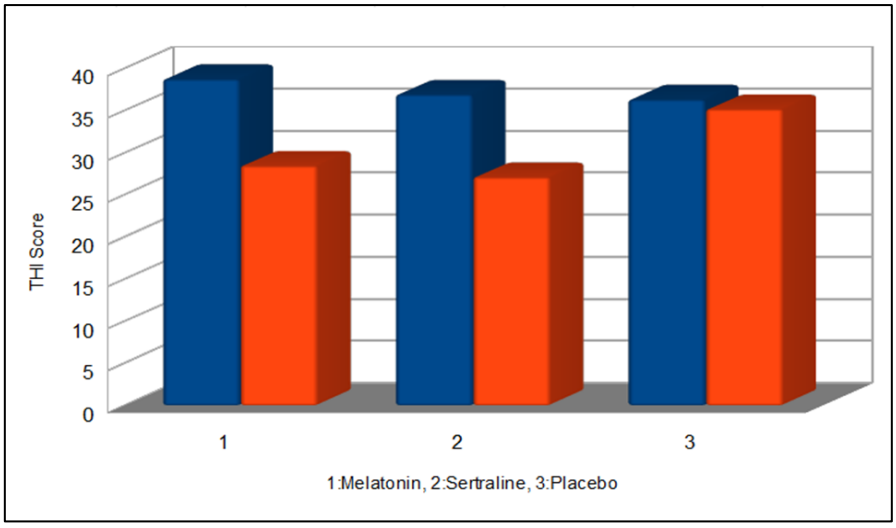

Figure 2. Comparison of THI in Melatonin, Sertraline, and placebo group.

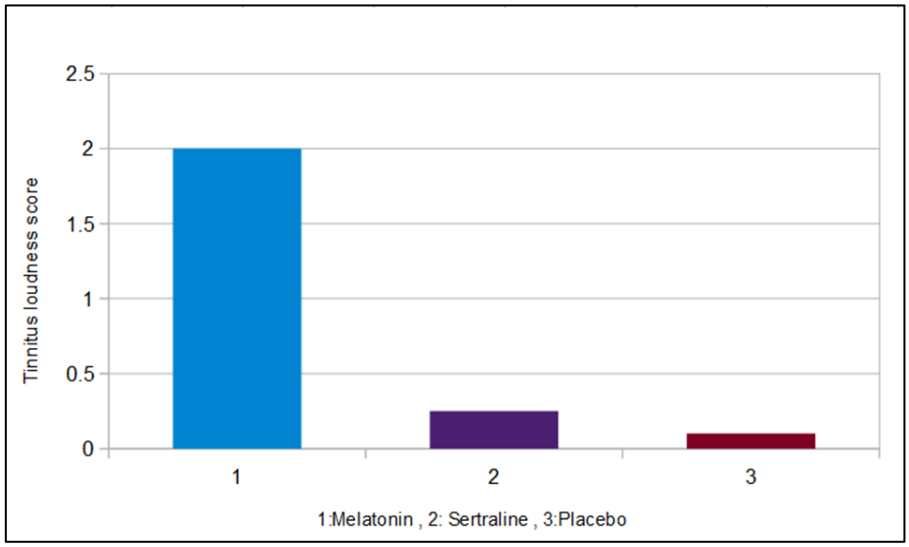

Figure 3. Comparison of tinnitus loudness score in Melatonin, Sertraline, and placebo group.

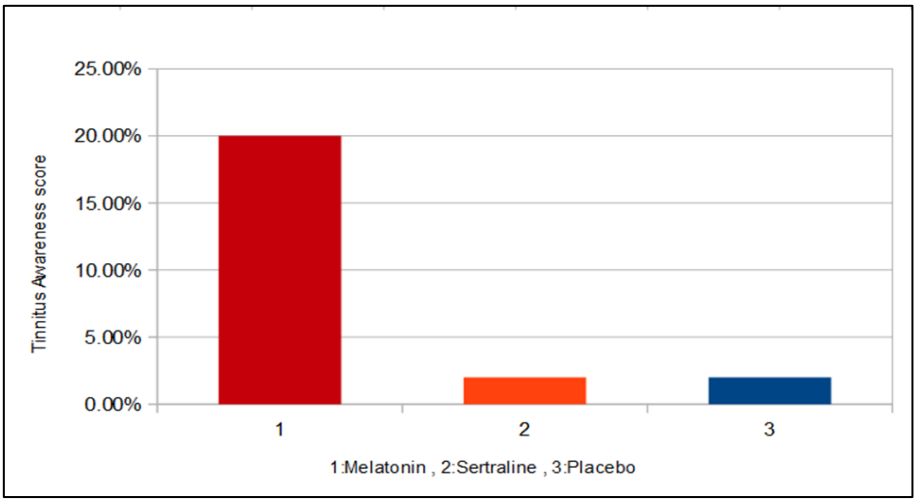

Figure 4. Comparison of tinnitus awareness score in Melatonin, Sertraline, and placebo group.

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Discussion

Melatonin is recognized as a valuable neurohormone produced by the pineal gland, which play a key role in the human body, including regulation of the sleep-wake cycle, blood pressure adjustment, and antioxidant effect (1). Pharmacological studies indicate that melatonin, rather than effects on patient's sleep, can also be protective against noise induced and drug induced hearing loss (11). In this regard, the effects of melatonin on tinnitus have been evaluated (9, 11). Moreover, melatonin demonstrated to be a safe and cost effective option in drug mediated ototoxicity caused by aminoglycosides and cancer chemotherapeutic agents (14) Along with these findings, melatonin limits subjective tinnitus in patients by a dosage of 3 mg daily (15). Furthermore, the effectiveness of melatonin in tinnitus was compared along with other agents, such studies demonstrated melatonin in conjunction with sulodexide and intratympanic dexamethasone is more efficient than Melatonin alone (17,18).

In addition, the tinnitus auditolimbic dopaminergic pathway results in many therapeutic concepts. With this in mind, Sulpiride and melatonin decrease dopamine activity and lead to decline tinnitus perception (11). Above all, the amount of sleep improvement was found to be related to tinnitus severity. Although Melatonin showed greatest impact on sleep improvement in patients with the worst sleep quality, the Melatonin effect on tinnitus was not associated with the tinnitus intensity (5). Besides, the melatonin advantages in the tinnitus treatment may be due to further neurogenerative features (15).

On the other hand, the effects of antidepressants on tinnitus investigated few studies reported no tinnitus perception as a side effect following antidepressant usage. Besides, no beneficial effect of antidepressant on tinnitus was reported (16, 17). Even so, there has been evidence indicating sertraline to be more effective than placebo in decreasing tinnitus severity. Likewise, improvement in tinnitus loudness was reported (10, 12). Given this fact, a significant relationship between the improvements in depressive and anxiety symptoms and decreasing of tinnitus was highlighted (12). Also, a significant improvement in tinnitus was reported with nortriptyline especially in the category of severe depression patients (11).

We found that, Melatonin and Sertraline both have valuable effects in the management of patients suffering from tinnitus. Our results signified their specific role in comparison with the placebo. On the contrary, there is also some conflicting evidence that raised doubts. Such reports mentioned, both Antidepressants and melatonin have no effects on tinnitus but they had no placebo allocation (18).

Conclusion

The results of the current study showed that both Melatonin and Sertraline significantly improved THI. However, Melatonin caused a 20% reduction in awareness of tinnitus and a two-fold decrease in tinnitus loudness, which according to the criteria considered by previous studies as the meaningful result, Melatonin significantly improved the tinnitus of the patients. In contrast, Sertraline resulted in a 2% reduction in awareness of tinnitus and a 25% reduction in tinnitus loudness, indicating no significant effect. Concerning the results of THI, both drugs were reported to be effective and useful but based on the level of awareness of tinnitus and loudness of tinnitus, Melatonin has positive outcomes, but Sertraline did not significantly improve these two criteria.

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Conflicts of Interest

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Ethics

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