ORIGINAL ARTICLE

The Effect of Melatonin on Tinnitus with Respect to Sleep and Depression: A Randomized Clinical Trial

Serap Koybasi, M. Hamid Boztas, Yusuf Ozgur Bicer, Erdinc Serin, Ahmet Emre Suslu, Yasemin Ongun Funda, Murat Sereflican

Abant Izzet Baysal University, Medical Faculty, Department of Otolaryngology, Bolu (SK, YOB, YOF, MS)
Abant Izzet Baysal University, Medical Faculty, Department of Psychiatry, Bolu (MHB)
Medistate Kavacık Hospital, Biochemistry Lab, Istanbul (ES)
May 29 Hospital, Department of Otolaryngology, Ankara (AES)

Objective: In this study we aimed to investigate the psychological status of tinnitus patients as well as the sleep quality and their relation to handicap caused by tinnitus using various scales. Additionally, serum melatonin levels and the effectiveness of melatonin treatment were studied.

Study Design: Prospective, double blind, randomized controlled trial

Materials and Methods: Patients were divided randomly into two groups as study (melatonin, n=13) and placebo (control, n=11) groups. Tinnitus Handicap Inventory (THI), Symptom Check List (SCL), Hospital Anxiety and Depression Scale (HAD), Beck Depression Inventory (BDI), Pittsburg Sleep Qualty Index (PSQI) were applied. After filling the scales and giving the venous blood sample for melatonin measurements the patients were instructed to take one tablet (placebo or 3 mg melatonin) before sleep every night. After 8 weeks, second order scales were filled and melatonin measurements were repeated.

Results: Serum melatonin levels were between 1-260 pg/ml; the mean was 38,7 pg/ml. The correlation of melatonin levels with THI and tinnitus duration was not significant. THI was found to correlate with different measures of the PSQI, HAD, and BDI in both groups. Statistical analysis failed to show any significant difference within and between groups in respect of anxiety, depressive symptoms and sleep as well as melatonin and handicap levels.

When the groups were assessed according to the THI severity (mild/moderate to severe;THI_2); in the control group there was significant differences in $PSQI_1$ and $PSQI_1$ (p=0.0008, p=0.18), HAD_1, HAD_2 (0.002, 0.03), HAD $Depression_{1-2}$ (0.0, 0.006) BDI (p=0.007) PSQI $_{2\ sleep\ disturbance}$ (p=0.018) parameters. However, in the melatonin group it was found that there were significant differences in $SCL_{2\ sleep\ latency}$, PSQI $_{2\ sleep\ duration}$ and total $PSQI_2$ parameters. (p=0.022, 0.027, 0.006 respectively)

Conclusion: Patients with higher handicap may benefit melatonin in respect of sleep latency and duration as well as sleep quality comparing with the patients taking placebo. Moreover, melatonin efficiency may be related to its antidepressive effect.

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Introduction

Chronic subjective tinnitus (thereafter termed tinnitus) defined as a sense of sound without external stimuli is a serious problem. Although about 35 % of adult population have had some experience with tinnitus, it is considered as a serious problem by 5-15% of the population [1-3]. Shargorodsky et al. in their recent study reported that 50 million US adults with tinnitus and 16 million of these to be frequent[4]. Older people, non Hispanic whites, former smokers and hypertensive patients were found to be at increased risk for tinnitus. It is a complex disorder in its genesis, perception and interpretation. It is a multilevel disease; not only the outer hair cells in cochlea but the limbic system, thalami nucleus, hippocampus and hypothalamic paraventricular nucleus were shown to take part in the process[5-11]. Current information about its etiology is unsatisfactory. Although a broad number of heterogeneous pathomechanisms and causes have been postulated no consensus has been reached to date[12]. Tinnitus usually accompanies hearing loss, aging,

Corresponding address:
Serap Koybasi
Abant Izzet Baysal University
Medical Faculty, Dept of Otolaryngology, Bolu/Turkey
E-mail: serapkoybasi@yahoo.com

noise exposure but may also be seen in normal hearing subjects[9].

While the majority of tinnitus patients can neglect its impact on daily life, for the others it may be a debilitating condition. Tinnitus has been reported to interfere with sleep and threaten the quality of life. It is also known to have comorbid psychological disorders[13]. Moreover, there are many reports regarding the effectiveness of psycopharmacologic treatment options in tinnitus. Melatonin a neurohormone mostly secreted by pineal gland in dark is a promising agent that was proposed both in tinnitus and depression[14-17].

In this study we aimed to investigate the psychological status of tinnitus patients as well as the sleep quality and their relation to handicap caused by tinnitus using various scales. Additionally serum melatonin levels and the effectiveness of melatonin treatment were studied in this respect.

Materials and Methods

Study design: Prospective, double blind, randomized controlled trial

Patients and groups: IRB approval obtained at the beginning of the study.

Adult patients (18-65 years of age) admitted with the complaint of tinnitus with a normal audiogram were accepted for this study. Following the signing of the informed consents the patients were included in this study. Patients with any type of hearing loss, having psychiatric illnesses or any chronic systemic disease were excluded from the study. Patients were divided randomly into two groups as study (melatonin) and control (placebo) groups by one of the investigators. Patients and other investigators were blinded with respect to the medication type. After filling the scales and venous blood draws for melatonin measurements the patients were instructed to take one tablet (placebo or melatonin accordingly) before sleep every night. After 8 weeks, the patients returned and the second order scales were filled and melatonin measurements were repeated.

Melatonin measurements: Venous blood was drawn after one hour sleep at night. Serum melatonin measurements were performed by enzyme-linked immunosorbent assay method using the Phoenix Melatonin ELISA reagents (Phoenix Pharmaceuticals, M5250, USA) on the Bio Rad Benchmark Plus Microplate Reader (BioRad Laboratories, Hercules CA, USA) and Thermoscientific Microplate Washer (Thermo Scientific, Hudson, NH, USA).

Scales: Tinnitus Handicap Inventory (THI), Symptom Check List (SCL), Hospital Anxiety and Depression Scale (HAD), Beck Depression Inventory(BDI), Pittsburg Sleep Quality Index (PSQI) were applied. The scores of scales were labeled as 1 and 2 representing the scores of the scales at the beginning and after the completion of the treatment respectively.

Statistical analysis: SPSS 17.0 program was used for the statistical analysis. Normality was tested with Shapiro-Wilk test. In case of normal distribution paired sample t test was used. One way anova and post hoc tukey test were used if more than two groups were analyzed. To test the difference within the groups Wilcoxon Signed Rank, between the groups Mann Whitney-U and Kruskal Wallis test were used if data had not normal variance. Categorical variables were compared using X^2 test. Correlations between variables were tested using Pearson's correlation test. $p<0.05$ was accepted as statistically significant.

Results

Thirty seven patients were included in the study. Of these 28 were female and 9 were male. The age was found to range between 18 and 60, and the mean was 39.2. The mean duration of the tinnitus symptom was 33.2 (2-240) months.

Serum melatonin levels ranged between 1-260 pg/ml and the mean was 38,7 pg/ml before any given treatment. THI scores were found to be between 4 and 84, and the mean was 35.4. The correlations of melatonin levels with THI scores and tinnitus duration was not significant.

Twenty four out of 37 patients returned for the second order scales and measurements; 13 to be in melatonin group and 11 in the control group. Because 13 patients did not returned to complete the study these patients were not included to study. The status of these patients without follow up regarding their anxiety and depression were seen to be statistically indifferent than the patients who complete the study ($p>0.05$). In respect of melatonin levels at the beginning, there was a statistically significant difference between groups (melatonin, control, and those without follow up). The difference was between the melatonin group and patients with no follow up ($p=0.038$). The melatonin levels were found to be higher in the melatonin group. There was no significant difference between melatonin and control group with respect to pretreatment serum melatonin levels. Table 1 summarizes melatonin levels, and the scores of THI together with other psychological scale of both control and melatonin groups.

Table 1. There is no significant difference between two groups with respect to age, melatonin levels and studied scales

	Control Group (n=11) (Mean)	Melatonin Group (n=13) (Mean)
Age	39.636	35.700
Serum Melatonin$_1$	38.886	14.838
Serum Melatonin$_2$	11.648	72.463
THI$_1$	27.091	39.077
THI$_2$	22.000	41.385
HAD$_1$	11.818	15.846
HAD$_2$	13.091	15.539
BDI$_1$	11.818	12.462
BDI$_2$	15.636	15.846
PSQI$_1$	5.091	5.923
PSQI$_2$	6.455	6.692

Concerning the correlations of the THI$_1$, in the melatonin group it was found to correlate with THI$_2$, daytime dysfunction score which is an item of PSQI and PSQI$_{1\text{-}2}$ global score in the melatonin group whereas in the control group statistical analysis revealed a correlation with BDI$_1$ scores and THI$_1$ (Table 2).

Table 2. Correlations of THI$_1$ in a) Melatonin and b) Control group

a)

Melatonin group THI$_1$	Pearson's Correlation (r)	Significance (p)
THI$_2$	0.776	0.002
Daytime dysfunction-2	0.611	0.026
PSQI$_2$	0.738	0.004

b)

Control group THI$_1$	Pearson's Correlation (r)	Significance (p)
Beck Depression Inventory-1	0.650	0.030

Regarding THI$_2$, in the melatonin group it was seen to correlate with THI$_1$, sleep latency-1 and 2 items of PSQI, PSQI$_1$ and PSQI$_2$. Similarly, sleep duration-2 and habitual sleep efficiency-2 items were seen to correlate to THI$_2$ (Table 3). In the control group even more correlations were found. Statistical analysis revealed significant correlations between THI$_2$ and PSQI$_1$, PSQI$_2$, HAD$_1$, HAD$_2$, BDI$_1$ total, SCL$_1$ total, somatic, ocd (obsessive compulsive disorder symptoms) and psychotic items of SCL$_1$ and SCL$_2$ and SCL sleep/eating item. Additionally sleep quality, daytime dysfunction items of the PSQI$_1$ and habitual sleep efficiency together with sleep disturbance items of PSQI$_2$ were found to have correlation with THI$_2$ as well as HAD1anxiety and depression items of HAD1 and HAD$_2$ (Table 4).

Table 3. Correlations of THI$_2$ in the melatonin group.

Melatonin group THI$_2$	Pearson's Correlation (r)	Significance (p)
THI$_1$	0.776	0.002
Sleep Latency-1	0.556	0.048
PSQI$_1$	0.594	0.032
Sleep Latency-2	0.708	0.007
Sleep Duration-2	0.705	0.007
Habitual Sleep Efficiency-2	0.650	0.016
PSQI$_2$	0.746	0.003

Table 4. Correlations of THI_2 in the control group.

Control Group THI_2		
	Pearson's Correlation (r)	**Significance (p)**
HAD_2 Total	0.743	0.009
SCL_1 Somatic	0.780	0.008
SCL_1 Depression	0.668	0.035
SCL_1 Psychotic	0.662	0.037
SCL_1 Sleep/Eating	0.844	0.002
SCL_1 Total	0.653	0.041
SCL_2 Somatic	0.651	0.030
SCL_2 OCD	0.645	0.032
SCL_2 Psychotic	0.614	0.045
BDI_1 Total	0.876	0.000
$PSQI_1$-C1 Sleep Quality	0.636	0.035
$PSQI_1$-C7 Daytime Dysfunction	0.849	0.001
$PSQI_1$ Total	0.739	0.009
$PSQI_2$-C4 Habitual Sleep Efficiency	0.696	0.017
$PSQI_2$–C5 Sleep Disturbance	0.731	0.011
$PSQI_2$ Total	0.633	0.037
HAD_1 Total	0.851	0.001
HAD_1 Depression	0.921	0.000
HAD_1 Anxiety	0.638	0.035
HAD_2 Depression	0.785	0.004

Statistical analysis failed to show any significant difference within and between groups in respect of anxiety, depressive symptoms and sleep as well as melatonin and handicap levels.

THI was assumed as mild in case the score was between 0-36 and moderate to severe in case it was between 38 and 100. We find that 9 patients in control group and 7 patients in melatonin group had scores less than 36 and the others more than 38. So only 2 patients in the control and 6 patients in the melatonin group have moderate to severe handicap level before any given treatment. When THI_2 scores were divided as mild and moderate to severe we could show interesting findings. There was statistically significant difference between the groups formed according to THI_2 mild/ moderate-severe with respect to sleep latency-1 (p= 0.018), $PSQI_1$ (p= 0.01), HAD_1 (p= 0.037), HAD1 depression score (p=0.019), sleep latency-2 (p= 0.0002), sleep disorder-2 score (p=0.045) and $PSQI_2$ (p= 0.001). The patients with higher THI_2 score were found to have more sleep and depressive symptoms.

When the groups were analyzed according to the THI_2 score it was found that; in the control group there was statistically significant difference in $PSQI_1$ and $PSQI_2$ (p=0.0008, p=0.18), HAD_1, HAD_2 (0.002, 0.03), HAD Depression 1-2 (0.0, 0.006) BDI (p=0.007) PSQI 2 sleep disturbance (p=0.018) parameters.

On the other hand in the melatonin group we found that there were significant differences in $PSQI_2$ sleep latency, $PSQI_{2\ \text{sleep duration}}$ and total $PSQI_2$ scores. (p=0.022, 0.027, 0.006 respectively) Patients with higher THI_2 scores were the patients with shorter sleep latency, longer sleep duration and better sleep (lower $PSQI_2$ scores). This result show that patients with high THI_2 scores can benefit melatonin in respect of sleep latency and duration as well as sleep quality comparing with the patients taking placebo. Moreover, we were able to show a statistically significant difference in THI_2 scores (p=0.034). Patients with higher THI_2 scores can benefit from melatonin more than the patients with low handicap levels.

In the control but not in the melatonin group the patients with higher THI_2 scores had higher scores in the parameters relating to depression. This finding let us think about the antidepressive effect of melatonin that it might put on the depressive symptoms. In the case the patients are grouped according to the THI scores, in the melatonin group $PSQI_2$ scores were found to be lower in patients with higher handicap level and $PSQI_2$ scores were found higher in the control. This finding might point to the positive effect of melatonin on sleep quality.

Linear regression analysis was performed to see the predictors of the post treatment handicap level. The results showed that in the control group HAD1 scores (p<0.001) and in melatonin group it was the sleep latency2 (p<0.01) that had the major effect on THI_2. This result again make us think that melatonin might show its effect via decreasing the depressive symptoms thus this finding may be attributed to the

reported antidepressive effect of melatonin in that dosage.

Discussion

Tinnitus is a complex entity with many aspects left to be clarified. There are many studies on this topic especially in the present decade.

Melatonin is advocated as a promising agent in tinnitus treatment [18]. The favorable effect of melatonin on tinnitus is attributed to its effect on improvement in sleep[15, 19], on regulation of the microcirculation[20] and its antioxidant property in the inner ear. However, there is no report about its serum level in tinnitus patients in the literature so far[14, 15, 18, 21] Shafil et al. reported higher melatonin levels in depressed adolescents[22]. In this study we wanted to enlighten if melatonin levels were related to handicap caused by tinnitus. According to our results, we could clearly say that it was not. Megwalu et al. in their open label study reported that melatonin use for tinnitus is associated with improvement[15]. In their study they also reported that the amount of improvement in sleep was found to be associated with that of tinnitus however the effect of melatonin was not associated with tinnitus severity. Furthermore, Rosenberg et al. reported a significant effect of melatonin on tinnitus. They stated that patients with higher THI scores and those with sleep difficulty were most likely to benefit from melatonin treatment[14]. In a recent study, Hurtuk et al. reported that 3 mg daily melatonin was associated with a decrease in tinnitus intensity and improvement in sleep quality in chronic tinnitus patients. [23] In contrary- although the same dose was used- according to our data, there is no direct significant effect of melatonin treatment on tinnitus in that dosage. The 3 mg of Melatonin po a day taken at night 1-2 hours before sleep is the dosing frequently used in related studies. It is the recommended dosing to stimulate the natural secretion of melatonin. As there is no consensus about the duration, we preferred 8 week period to see a possible effect. There are some studies about strengthening the reported effect of melatonin on tinnitus. Neri et al combined melatonin and sulodexide -which is known to increase the inner ear blood flow- to see the effect on tinnitus[20]. They reported that the combination was better than melatonin alone in decreasing handicap level. Gonzalez- Lopes et al. reported melatonin combined with sulpiride which is an antidopmaninergic agent to be more effective than melatonin alone[24].

In this study we used THI that was adapted to Turkish language [25, 26]. It is widely used in clinical context to asses tinnitus related handicap and the effect of treatment. Its usage is advocated to asses the tinnitus handicap because of its high internal consistency of the total score [27]. In this study tinnitus handicap level was found to be irrelevant to the duration of tinnitus.

Sleep disturbance is a common and frequent complaint reported by tinnitus sufferers. Recent studies have shown that when insomnia and depression are associated with tinnitus there is decreased tolerance and increased discomfort with the tinnitus [28-30]. Asplund R. reported a close interrelationship between tinnitus, sleep, and sleepiness in elderly[28]. Sylvie et al showed that tinnitus patients have greater self reported sleep difficulties specifically in sleep efficiency and quality, and that higher tinnitus related distress was associated with greater sleep disturbance[31]. The effectiveness of Melatonin in tinnitus is also reported to correlate with the degree of relief in sleep difficulties [14, 15]. Beside sleep disturbances, an association between tinnitus and psychological distress has been reported in many studies[32-34]. Sulvian et al. had been reported a lifetime prevalence of 78% for depression and it was 60 % at the time of the interview[35]. Anxiety and mental health problems are other psychological aspects in tinnitus patients. Norun Krog et al. in their general population study reported that participants with tinnitus have had scored significantly higher on anxiety and depression and lower on self esteem and well-being than people without tinnitus and concluded that there was an association between tinnitus and mental health[36].

Agomelatine has been advocated in depression[21] and it was shown to be a potent agonist of Melatonin receptors (MT1 and MT2) with $5HT_{2c}$ antagonist properties [37]. This mechanism of action was reported

to be related to the efficacy on depression and on the regulation of associated sleep disorders in depression[38]. The efficacy of 25mg agomelatine in treating major depression has been shown in many randomized and controlled studies [39-41]. It is reported that 25 mg agomelatin can be increased to 50 mg in case it is ineffective and to be well tolerated[39]. The major side effect is headache. These properties make melatonin as a promising agent in tinnitus management as tinnitus is associated both depression and sleep disturbances. One important thing is the dosage. In our study we used only 3mg for tinnitus but perhaps it would be better to increase the dose to see its efficacy on tinnitus.

We showed that melatonin may help reduce the depressive and sleep related symptoms in patients with moderate to severe THI scores. Unlike Megwalu et al., Rosenberg et al. in their prospective randomized double blinded study reported that the effect of melatonin on tinnitus was related to the THI level[14, 15]. According to their report the patients with higher THI score were more likely to improve with melatonin. Unfortunately in our study group the patients with higher THI scores were less in number. The patients included in the study were seen to have mild disease mostly. We think that with a larger number of severe handicapped patients this study might show more significant effect of melatonin on tinnitus.

In our study too, we found an association between sleep disturbance and tinnitus handicap level.

Regarding the pretreatment measurements THI scores were found to correlate with depressive symptoms and sleep disturbance in the control and melatonin group respectively. Looking at the post treatment scores it was seen to correlate with depression and sleep related symptoms in the control and only sleep related symptoms in the melatonin group. These results may be attributed to the antidepressive effect of Melatonin. At this point these results are in accordance with the results in the literature.

In conclusion, this study shows that serum melatonin levels are irrelevant to the handicap caused by tinnitus. Melatonin in 3 mg per day per oral was seen to be insufficient by itself to improve tinnitus. Instead, it was shown that melatonin even in that dosage can show its effect on sleep and depression those shown to be associated with tinnitus. The authors believe that in case the number of moderate to severe tinnitus patients increased, the results would be stronger. Seeking of the efficient treatment modality of tinnitus continues.

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