Evaluating the Effects of Agomelatine on Polysomnography Parameters in Patients with Obstructive Sleep Apnea.

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ABSTRACT -- Purpose: Obstructive sleep apnea (OSA) is a common serious sleep disorder. Melatonin-based drugs such as agomelatine may have beneficial effects on patients with sleep disorders. This study aimed to evaluate agomelatine effects on polysomnography parameters in patients with OSA. **Methods**: In this randomized, parallel, and single-blind study, seventy patients 18 years of age or older with obstructive sleep apnea who were referred to the sleep clinic were evaluated. The patients were randomly assigned into agomelatine and control groups. Patients in the agomelatine group received 50 mg agomelatine, one hour before sleep, for three consecutive nights prior to the polysomnography test, while the patients in the control group did not receive agomelatine. Sleep test parameters were compared between the two groups. **Results**: Three parameters in the agomelatine versus control group showed significant differences. They were the median and interquartile range of the total sleep time, 397 [326.5-437.4] vs. 287.5 [184-393.1; *p*, 0.004] minuets, sleep efficiency percentage, 75.6 [71-87.4] vs. 65.1 [50.8-80.1; *p*, 0.005] and the wakening percentage, 7.5 [12.01-27.6] vs. 8.8[18.3-49; *p*, 0.004] agomelatine vs. control group. Other polysomnography parameters revealed no significant differences between the two groups. **Conclusions**: Agomelatine administration in patients with OSA may improve total sleep time, sleep efficiency percentage and the percentage of patients' awakening.

INTRODUCTION

Obstructive sleep apnea (OSA) is a common serious sleep disorder characterized by recurrent episodes of decreased airflow during sleep due to the upper airway's complete or incomplete obstruction (1).

OSA has many complications, including cardiovascular events, neurocognitive effects, motor vehicle accidents, and insomnia. Among patients with sleep apnea-related symptoms, the co-occurrence of insomnia has been reported to vary between 6 and 84%, indicating that comorbid insomnia and sleep apnea (COMISA) have been observed in a considerable number of patients (2,3). Fragmented, non-restful sleep in these patients leads to symptoms such as morning headache and drowsiness, which can impress patients' quality of life. Therefore, taking a rational and safe approach to ameliorate the problem and proper clinical management of COMISA patients is essential. Thus far, studies on benzodiazepines have documented that although they are effective in relieving sleep problems, they may not be optimal choices for OSA patients due to respiratory system suppression, disruption of the typical sleep rhythm, and the potential for dependence and addiction (4,5).

GLOSSARY. **AHI**, Apnea-hypopnea index is the total number of apneas and hypopneas per hour of sleep; **RDI**, Respiratory disturbance index is the total number of apneas, hypopneas, and respiratory effort–related arousals per hour of sleep; **TST**, total sleep time is total time asleep after lights out; **SPT**, sleep period time is the sum of the total sleep time and awakening time; **Sleep efficiency**, the percentage of time a person sleeps, compared with the amount of time a person spends in bed; **PLM**, periodic leg movement is the number of events that indicate a neurological disorder with repetitive leg movements during sleep; **PLMI**, periodic leg movement index is the number of repetitive leg movements per hour of sleep; **Arousal index**, all events that cause a change in the patient's EEG per hour of sleep, these events can wake a person up or change REM sleep to non-REM sleep; **PLM arousal index**, is the all PLM events that caused the arousal per hour of sleep.

A previous study confirms that melatonin improves the duration and quality of sleep in chronic obstructive pulmonary disease (COPD) patients with sleep problems (6). Agomelatine and ramelteon are both agonists of melatonin receptors. Agomelatine is an MT_1 and MT_2 melatonin receptors agonist and a 5-HT_2C receptor antagonist with a half-life of 2.3 hours (7) and an approximately equal affinity for both melatonin receptors, while ramelteon has a much greater affinity for the MT_1 receptor (8). The MT_2 receptor produces a phase-shifting action on the circadian rhythm.

The pathophysiology of COMISA has not been determined precisely, but it is hypothesized that insomnia in OSA patients is probably caused by phase-shifting and improper melatonin peak (9). For the aforementioned explanations, agomelatine may be more effective than ramelteon in reducing insomnia problems in OSA patients.

Agomelatine, which is a potent agonist of MT_1 and MT_2 melatonin receptors, as well as 5-HT_2C receptor antagonist, seems to maintain and improve sleep and mood simultaneously and helps to maintain alertness throughout the daytime, without causing daytime sedation. Also, its half-life is longer in comparison with melatonin (2.3 hours vs. 30-45 minutes, (8,10)). Because of melatonin's short half-life (<30 min), its effectiveness in enhancing and maintaining sleep has not been identified in different studies. Thus, the need for the development of prolonged release preparations of melatonin or melatonin agonists with a longer duration of action like agomelatine on sleep regulatory structures can have clinical significance (10).

Mi et al. (11) study findings indicated that after 8 weeks of using agomelatine in depressed patients, TST and sleep efficiency were enhanced, while awakenings throughout the sleep were reduced, also a review of several studies by Dubovsky et al. (12) suggests that agomelatine improves the duration of sleep as well as patients' mood. The study aimed to evaluate the effect of agomelatine on polysomnographic parameters and insomnia in OSA patients.

MATERIALS AND METHODS

Setting. This is a randomized, parallel, and blinded outcome assessor study conducted in the sleep clinic of Dr. Masih Daneshvari Hospital, Tehran, Iran. The study timeframe was from June to October 2021.

Patients. Seventy patients aged 18 years and older with OSA were recruited in the study. The exclusion criteria were as follows: pregnancy, breastfeeding, neurological diseases (stroke, epilepsy, tumor, and previously neurological manipulation), use of stimulant drugs and all medications that affect sleep, history of allergy to agomelatine or other formulation components, patients with stage 2 or 3 of liver failure and history of diseases that affect sleep, ciprofloxacin or fluvoxamine consumption. We selected patients based on the eligibility criteria (Apnea-hypopnea index (AHI) greater than or equal to 5 measured by polysomnography) in the sleep clinic of Dr. Masih Daneshvari hospital.

Interventions. Patients were randomly divided into the agomelatine and the control groups (Outcomes. After polysomnography, parameters, including AHI, respiratory disturbance index (RDI), total sleep time (TST), sleep period time (SPT), sleep efficiency, sleep onset, rapid eye movement (REM) latency, number of REM cycles, periodic leg movement (PLM), periodic leg movement index (PLMI), stage 1 non-REM sleep duration, stage 2 non-REM sleep duration, stage 3 non-REM sleep duration, REM duration, percentage of patient's awakening, arousal index, PLM arousal index, and minimum oxygen saturation were compared between the two groups.

Statistical analysis. Sample size was calculated using GPower version 3.1 software. We considered sleep onset to be 5 minutes for agomelatine and 9 minutes for the control group. Considering an alpha error of 0.05 and 80% power and potential drop-out rate, 35 participants were calculated in each group.

The SPSS version 26.0 software (IBM Corp., Armonk, NY, USA) was used for statistical assessment. Primarily, the normality of data distribution was evaluated by the Shapiro-Wilk test. To compare the differences in the quantitative variables between the two groups, the Student's t-test or Mann-Whitney U test was performed. The distribution of data regarding the number of REM cycles, N2 duration, and REM duration was normal. Hence, the Student's test of t-test was performed to

). For randomization, the block randomization technique was used. Eighteen blocks, including five patients, were generated by the Online Randomizer website (https://www.sealedenvelope.com/simple-randomiser/v1/). In the agomelatine group, patients received 50 mg agomelatine (Tadbir Kalay-e Jam®,

Tehran, Iran) one hour before sleep for three consecutive nights prior to the test. The control group did not receive agomelatine. Patients in both groups underwent polysomnography test. We used diagnostic overnight polysomnography at the sleep clinic (type 1 sleep study).

Outcomes. After polysomnography, parameters, including AHI, respiratory disturbance index (RDI), total sleep time (TST), sleep period time (SPT), sleep efficiency, sleep onset, rapid eye movement (REM) latency, number of REM cycles, periodic leg movement (PLM), periodic leg movement index (PLMI), stage 1 non-REM sleep duration, stage 2 non-REM sleep duration, stage 3 non-REM sleep duration, REM duration, percentage of patient's awakening, arousal index, PLM arousal index, and minimum oxygen saturation were compared between the two groups.

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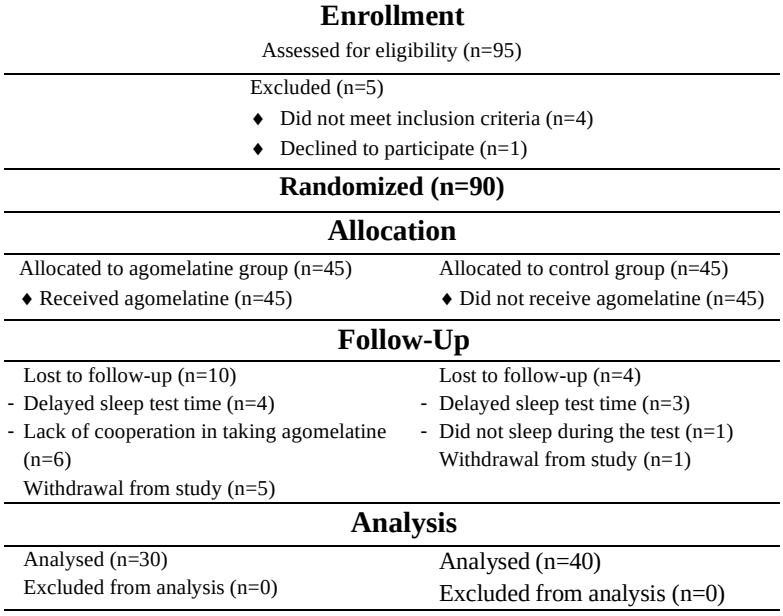

Figure 1. Consort flowchart

assess the statistical difference. However, the data regarding other parameters were not normally distributed. Hence, the non-parametric test of Mann-Whitney U was performed to assess the statistical difference. Normally distributed data were reported as mean ± standard deviation and data with non-normal distribution were reported as median and interquartile range. The statistical tests performed for each parameter are listed in Table 2. $p < 0.05$ was considered statistically significant in the whole test.

Ethics approval. The study was approved with the ethics code number of IR.SBMU.PHARMACY.REC.1398.280 by the Iran national committee for ethics in biomedical research and was registered in Iranian Registry of Clinical

Trials with the registration number of IRCT20151227025726N26. All procedures performed in this study were in accordance with 1964 Helsinki declaration and its later amendments.

RESULTS

From 95 patients who were eligible for the study, initially, 5 patients were excluded due to not meeting the inclusion criteria or declining to participate in the study. Subsequently, 14 patients were lost to follow-up for several causes, and six withdrew from the study. Finally, 30 patients in the agomelatine group and 40 in the control group were analyzed for further evaluation. Patients demographic characteristics were compared, as shown in Table 1.

Table 1. Comparison of the clinical and demographic data between the agomelatine and control groups.

Variable	Agomelatine N=30	Control N=40	P
Age (year)	55.4 ± 14.55	58.8 ± 14.6	0.40
Sex (male)	21 (70%)	26 (65%)	0.94
BMI (kg/m^2)	31.5 ± 7.10	32.3 ± 6.4	0.20
Diabetes	8 (26.66%)	7 (17.5%)	0.70
Hypertension	15 (50%)	17 (42.5%)	0.06
Depression or Anxiety	10 (33.33%)	13 (32.5%)	0.40
Smoking history	9 (30%)	10 (25%)	0.80
Asthma or COPD	0 (0%)	1 (2.5%)	0.20

Values are shown as a range (mean ± SD) for numerical data and numeral only for non-numerical data.

Table 2 Comparison of the Polysomnography parameters in the agomelatine and control groups.

Parameter	Agomelatine group	Control group	*p*	Test
AHI (event/hour)	35.4 [24.7-63.8]	31.3 [21.7-48]	0.291	M
RDI (event/hour)	35.4 [24.7-64.1]	31.3 [21.7-51.4]	0.250	M
TST (minute)	397 [326.5-437.4]	287.5 [184-393.1]	0.004	M
SPT (minute)	490 [436-511.5]	465 [280-516.1]	0.211	M
Sleep efficiency (percentage)	75.6 [71-87.4]	65.1 [50.8-80.1]	0.005	M
Sleep onset (minute)	8.5 [2-20.6]	10.2 [3-14.6]	0.631	M
REM latency (minute)	105 [86.5-160]	130.5 [90-252]	0.379	M
Number of REM cycles	4.51±5.05	3.60±2.87	0.434	T
PLM (event)	0 [0-1]	0 [0-0]	0.702	M
PLMI (event/hour)	0 [0-1]	0 [0-0]	0.721	M
N1 duration (percentage)	20.52 [16.81-27.6]	18.8 [13.1-26.1]	0.674	M
N2 duration (percentage)	51.47±12.11	47.78±15.29	0.281	T
N3 duration (percentage)	7.5 [4.1-15.4]	8.8 [0-19.01]	0.737	M
REM duration (percentage)	11.16±7.5	14.23±10.18	0.169	T
Awakening percentage	7.5 [12.01-27.6]	8.8 [18.3-49]	0.004	M
Arousal index (event/hour)	15.3 [9.5-22.8]	10.1 [5.5-17.7]	0.138	M
PLM arousal index (event/hour)	0 [0-0]	0 [0-0]	0.374	M
Min O_2 saturation (percentage)	78 [50-86]	78 [62-80]	0.717	M

In the parameter column, AHI: apnea hypopnea index (event/hour); RDI: respiratory disturbance index (event/hour); TST: total sleep time (minute); SPT: sleep period time (minute); Sleep efficiency: percentage; Sleep onset: minute; REM latency: minute; PLM: periodic leg movement (event); PLMI: periodic leg movement index (event/hour); N1 duration: stage 1 non-REM sleep duration (percentage); N2 duration: stage 2 non-REM sleep duration (percentage); N3 duration: stage 3 non-REM sleep duration (percentage); REM duration: percentage; Arousal index: event/hour; PLM arousal index: event/hour; Min O2 saturation: percentage. In the Test column, M: Mann-Whitney U test; T: Student's t-test.

Polysomnography parameters were compared between the two groups (Table 2). The data distribution was normal regarding the number of REM cycles, N2 duration, and REM duration. However, the data regarding other parameters were not normally distributed. Overall, according to the p-values, only TST, sleep efficiency, and awakening percentage had significant differences between the two groups. TST had a longer duration, sleep efficiency percentage significantly increased while patients' awakening percentage had a substantial decrease in the agomelatine group (Table 2, Figure 2). On the other hand, AHI, RDI, SPT, sleep onset, REM latency, the number of REM cycles, PLM, PLMI, stage 1 duration, stage 2 duration, stage 3 duration, REM duration, arousal index, PLM arousal index, and minimum oxygen saturation had no significant differences between the two groups.

DISCUSSION

In this study, comparison of polysomnography parameters between the two groups revealed a significant improvement in TST, sleep efficiency, and the percentage of patients' awakening in the agomelatine group. Also, the statistical

significance despite medians overlap in the percentage of patients' awakening can be rational considering the wide difference of the interquartile range of the control group, which indicates a longer duration of awakening in patients of the control group. Therefore, we suggest that agomelatine could maintain sleep integrity and prevent sleep deficiency which is a very important effect in a broad range of OSA patients that suffer from insomnia and sleep fragmentation that causes impairment of physical and mental health.

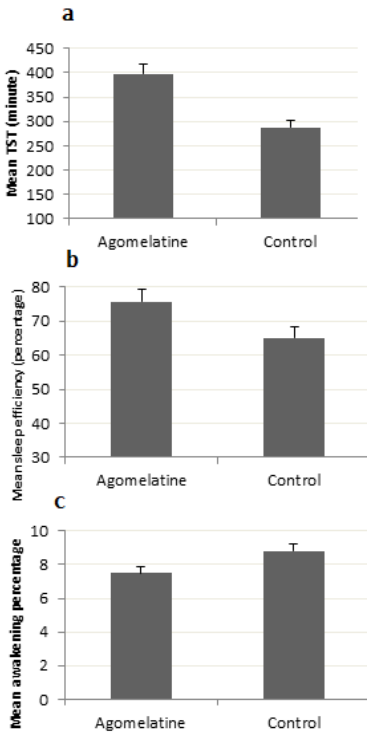

Figure 2. Comparison of mean TST (minute) in chart 1, mean sleep efficiency (percentage) in chart 2, and mean awakening percentage in chart 3 between agomelatine and control groups. In the agomelatine group, TST has a longer duration (*p*, 0.004), Sleep efficiency percentage significantly increases (*p*, 0.005) and the percentage of patients' awakening has a considerable decrease (*p*, 0.004).

A study by Mi et al. (11) that investigated the effects of agomelatine and mirtazapine on sleep disturbance indicated that after 8 weeks of using agomelatine or mirtazapine in 27 depressed patients, TST and sleep efficiency were enhanced, while awakenings throughout the sleep were reduced in both groups. The targeted population in the mentioned study was patients with the diagnosis of major depressive disorder, while we studied patients with OSA. The intervention also differed from our study, which was agomelatine compared to mirtazapine. We studied agomelatine compared to the control group. The dose and duration of agomelatine therapy were also different. Despite the differences between the two studies including the sample size, the mentioned results are parallel with the results of the present study.

Studies have shown that benzodiazepines (as the most commonly prescribed medicines for insomnia), like agomelatine, improved TST and insomnia (13). However, according to the previous trials, benzodiazepines are REM sleep suppressants and as it is acknowledged, REM sleep has a great impact on the learning process and memory (14). Moreover, benzodiazepines are known to reduce stage 3–4 sleep and in some cases stage 1 as well as to cause dependence and addiction (5,15). They can prolong the duration of sleep-disordered breathing (SDB) events or cause breathing difficulties during sleep. In addition, the risk of OSA is higher among patients treated with benzodiazepines (16,17). Conversely, based on the outcomes of our study, the use of agomelatine in OSA patients did not cause changes in sleep patterns. It did not cause or increase the incidence of respiratory attacks. Therefore, it may have less harmful effects on OSA patients. Furthermore, the use of benzodiazepines, contrary to what we saw with agomelatine, is associated with lower minimum oxygen saturation in patients with OSA (18). Considering the above information, benzodiazepine prescribing in OSA patients can be associated with severe complications.

A review of all available studies up to 2018 has shown that using melatonin, like agomelatine, can increase TST and improve sleep quality and onset (19). In our study, sleep onset in the agomelatine group was earlier than in the control group, but there was no statistically significant difference between the two groups. According to a systematic review by Kuriyama et al. (20), using ramelteon, similar to the results of our study, improved TST and sleep efficiency and reduced the awakening duration during sleep. Another trial has also shown that treatment with prolonged-release melatonin (PRM) can improve REM sleep behavior disorder (RBD, a REM-sleep parasomnia) in OSA patients (21). However, according to previous studies, PRM has

been found to be more effective in insomnia management in the elderly population (22).

The average number of REM cycles during normal sleep is 5. In this study, the average number of REM cycles in the agomelatine group was almost equal to the number of cycles in normal sleep and was not statistically different from the control group. The REM stage is essential due to its relation to several physiological and psychological phenomena (23). Agomelatine has not been impacted negatively in terms of the number of cycles in our study.

Altinyazar et al. (24) reported a case which showed that taking agomelatine (25 mg/day) following discontinuation of lorazepam improved insomnia in a 91-year-old woman with Alzheimer's. Cognitive impairment and daily function were also improved and in addition, the number of awakenings during sleep and drowsiness were reduced throughout the day at 1 month. Patients' liver function tests were monitored during the use of agomelatine as recommended in the drug leaflet (after 3 weeks of treatment with agomelatine, a liver function test is suggested) and no side effects were observed. The duration and the dose of agomelatine were different from the present study but regardless of the differences between the two studies, the mentioned insomnia-related results are similar to the results of our study.

As a limitation of the study most of the statistical tests performed in the study were non-parametric (Mann-Whitney U). Hence, estimating clinical significance and effect sizes including mean differences or standardized mean differences were not feasible. However, considering the low-power in non-parametric tests, we believe that a significant p-value in a non-parametric test has a considerable effect size.

CONCLUSION

Short-term use of agomelatine in patients with OSA could increase TST and sleep efficiency. Furthermore, it reduces the percentage of awakenings during the night sleep, and contrary to other frequently used insomnia medications, agomelatine did not disturb sleep patterns and did not increase apnea attacks, leg movements, and arousal index. Also, agomelatine did not significantly alter oxygen saturation between the groups. All of these point to the fact that using agomelatine may be superior to other hypnotics in patients with OSA and insomnia due to its favorable therapeutic effects. However, further research is needed because of several limitations, such as the small sample size, short-term use of the drug, and the lack of placebo in this study.

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DECLARATIONS

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Availability of data and material. The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions. Behnaz Gholizadeh Niari, Parisa Adimi Naghan, and Farzaneh Dastan: Conceptualization, Methodology, Data Collection, and Writing- Original Draft; Raha Eskandari: Writing-Review & Editing; Saghar Barati: Data Analysis. All authors approved the final version of the manuscript.

Consent to participate and publish. Informed consent was obtained from all participants included in this study, and all patients signed informed consent regarding publishing their data.

Conflicts of interest. The authors declare that they have no conflict of interest.

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