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Polysomnographic Pattern of Melatonin Therapy in Perimenopausal Women

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Abstract

Background: Earlier, we described our own study results of the chronobiological circadian rhythm of salivary fluid melatonin secretion in menopausal women, which allowed us pathogenetically to substantiate the use of melatonin drugs for insomnia in the perimenopausal period. The aim of this research was to evaluate the sleep quality using polysomnographic monitoring in perimenopausal women with sleep disorders (SDs) before and after 3 months of melatonin therapy.

Methods and Results: The study involved 21 perimenopausal women with complaints of SDs. All women completed a questionnaire to assess the subjective severity of insomnia (Insomnia Severity Index, ISI) and underwent a clinical-anamnestic and gynecological examination. Polysomnography (PSG) was performed before and after 3 months melatonin therapy in a daily dose of 3 mg. After melatonin intake, PSG demonstrated improvement in sleep latency, overall sleep efficiency, and an increase of REM sleep. A statistically significant number of EEG activation reactions indicate a decrease in sleep fragmentation and an improvement in sleep segmental structure.

Conclusions: The use of melatonin in a dose of 3 mg/day for 3 months is one of the main methods for treatment of SDs in age-related estrogen-deficient situations. The main clinical effect, which significantly improves the quality of life, is associated with the elimination of pre- and intrasomnic disorders. (**International Journal of Biomedicine. 2020;10(2):161-164.**)

Key Words: polysomnography • melatonin • perimenopausal women • sleep • insomnia

Abbreviations

AHI, the apnea-hypopnea index**; EOG**, electrooculography; **EMG**, Electromyography; **ISI**, the insomnia severity index; **PSG**, polysomnography; **SDs**, sleep disorders; **REM**, rapid-eye-movement; **SWS**, slow-wave sleep; **WASO**, wake after sleep onset

Introduction

The onset of menopause is one of the critical periods in a woman's life. According to a number of studies, from 25% to 50% of women in the menopausal period report sleep-related problems, compared with 15% of women of fertile age.[1] It has been shown that sleep efficiency indicators decrease with age and sleep latency, wakefulness time during sleep (WASO) increases, and REM sleep time significantly decreases.[2] However, the famous Wisconsin Sleep Cohort Study,[3] which included 589 premenopausal, perimenopausal, and postmenopausal women, showed that menopausal status was moderately related to self-reported dissatisfaction with sleep but was not consistently associated with symptoms of insomnia or sleepiness. Symptoms and signs of sleep abnormalities in midlife women should not be attributed primarily to menopause before ruling out underlying sleep disorders.

It is well known that women are more likely to suffer from insomnia than men are.[4] This fact has been noted since the menarche period, and with the development of age-related

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estrogen deficiency, gender differences in the frequency of insomnia disorders become more and more significant. Most scientists attribute this to hormonal and metabolic changes that occur in a woman's body at the onset of menopause. The regulatory role over circadian biorhythms is assigned to be produced by the epiphysis melatonin hormone.[5-7] Age-related features are not only a decrease in the level of melatonin secretion, but also a change in the daily time curve of this hormone production.[8,9] All these data made it possible to substantiate pathogenetically the use of melatonin in the treatment of SDs in various pathologies. There is a scientific rationale for proposing melatonin-agonists as an adjunctive treatment of mood stabilizers in treating SDs in bipolar disorders.[10] Thus, the effectiveness of melatonin has been repeatedly shown in SDs in cerebral vascular insufficiency.[11] The use of melatonin in gynecology showed a decrease in the intensity of autonomic disorders in menopausal syndrome.[12]

Earlier, we described our own study results of the chronobiological circadian rhythm of salivary fluid melatonin secretion in menopausal women, which allowed us pathogenetically to substantiate the use of melatonin drugs for insomnia in the perimenopausal period.[13,14] The need to objectify the effectiveness of melatonin therapy using instrumental methods determined the purpose of the study: Comparative assessment of sleep quality using polysomnographic monitoring in perimenopausal women with SDs before and after 3 months of melatonin therapy.

Materials and Methods

The study involved 21 perimenopausal women with complaints of SDs who were referred by a gynecologist-endocrinologist to the Somnology Center of the Scientific Center for Family Health and Human Reproduction Problems (Irkutsk, the Russian Federation) from 2016 to 2018. Patients complained of SDs for 6 months or more, repeated at least 4 or more nights per week in the form of difficulty falling asleep (more than 20 minutes from the time the lights turned off) and frequent night awakenings (at least 2-3 episodes per night). All women completed a questionnaire to assess the subjective severity of insomnia (Insomnia Severity Index, ISI)[15] and underwent a clinical-anamnestic and gynecological examination. After the examination, melatonin therapy was administered for 3 months in a dose of 3 mg once daily, 30 minutes before bedtime. All women completed the study, and the effectiveness of melatonin therapy was evaluated by PSG.

Inclusion criteria were age 45-55; oligomenorrhoea or amenorrhea during last 12 months; a basal level of follicle-stimulating hormone (FSH)>20 IU/ml; ultrasounds criteria: 1) endometrial dysfunction: mismatch of structure and thickness corresponding to the first and the second phases of the menstrual cycle; 2) ovarian follicle reserve depletion

Exclusion criteria were hormone replacement therapy and the use of drugs affecting melatonin secretion ; decompensation of cardiovascular, mental, neurological, and endocrine diseases; an exacerbation of chronic diseases; presence of chronic SDs in the past; hypnotics administration during the last two weeks.

The polysomnographic monitoring was carried out in a specially equipped laboratory, using the GRASS-TELEFACTOR Twin PSG (Comet) system with an As 40 amplifier with the SPM-1 integrated sleep module (USA), according to the standard methodology. During sleep, the EEG was recorded from central (C3-A2, C4-A1) and occipital (O1-A2, O2-A1) derivations; the EOG was recorded from electrodes placed lateral to the outer canthus of each eye, slightly above (right eye) and below (left eye) the bi-canthal plane, and referenced to the contralateral mastoid electrode (A1 or A2); the EMG was recorded with electrodes placed on the chin and submentally. The ECG was recorded using one standard lead. The oro-nasal breathing airflow was recorded using a thermocouple generating an electrical signal in response to fluctuations in the air temperature during breathing. The thoracic and abdominal breathing efforts were recorded through piezoelectric sensors generating an electrical signal in response to stretching of the elastic fixation belt. The degree of blood oxygen saturation (pulse oximetry) was determined by applying a special sensor to the finger of the subject. Sensors were also applied to record snoring episodes and the patient's body position during sleep.

Statistical analysis was performed using STATISTICA 6.1 software (Stat-Soft Inc., USA). For descriptive analysis, results are presented as mean±standard deviation (SD). Categorical variables were analyzed using the Chi square test. The Wilcoxon criterion was used to compare the differences between the paired samples. Group comparisons with respect to categorical variables were performed using the Chi square test or, alternatively, Fisher's exact test when expected cell counts were less than 5. A probability value of $P<0.05$ was considered statistically significant.

The study was carried out in compliance with Ethical Principles for Medical Research Involving Human Subjects, Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013. The study was approved by the Ethics Committee of the Scientific Center for Family Health and Human Reproduction Problems. Written informed consent was obtained from each patient.

Results

Table 1 presents comparative data from an anamnestic study before and after 3 months of using 3mg of melatonin 30-40 minutes before bedtime. The results of the clinical and anamnestic examination demonstrate a high percentage of a combination of pre-, intra- and postsomnic disorders. Moreover, only one patient complained only of difficulty falling asleep. Taking into account the data on the assessment of the subjective severity of insomnia, the mean value of ISI was determined. Thus, before treatment, the ISI value was 21.3±0.54, which corresponds to SDs of moderate severity. It is noteworthy that the subjective perception of one's sleep after taking the melatonin preparation was noticeably changed. Thus, complaints of presomnic disorders persisted only in 2 women who perceived the proper period of falling asleep for 5-7 minutes. Complaints of a combination of pre-

and intrasomnic disorders persisted in only 2 women. Thus, the objectification of the overall picture of sleep using a diagnostic study in the sleep laboratory was the next step in evaluating the effectiveness of melatonin.

Table 1.

Data from an anamnestic study before and after 3 months of melatonin therapy

Variable	Before melatonin therapy	After melatonin therapy
Age, yrs	51.2±4.7	52.1±5.1
BMI, kg/m^2	27.09±1.56	26.3±1.2
Incidence of major SDs (%): - difficulty falling asleep - night awakenings (more than 2 episodes per night) - difficulty morning awakening - combination of 2 and/or 3 manifestations of insomnia	 10-58.8 9-52.9 13-76.4 16- 94.1	 2- 11.7 3-17.6 5-29.4 2-11.7
ISI	21.3±0.54	10.1±2.1*

*- *P<0.05*

According to the PSG study, the total study time in all patients was 7-8 hours of nighttime sleep. An analysis of the information obtained made it possible to determine the duration of Stages 1 and 2 of SWS, Stage 3 of SWS, and the phase of REM sleep in minutes. Attention was also paid to indicators of overall sleep efficiency, estimated as the ratio of total sleep time to total recording time, expressed in percentage, latency to sleep, and WASO indicators. AHI, EEG arousal reactions, and percentage oxygen saturation of the blood (SaO_2) during night sleep were evaluated. The results of the PSG study are presented in Table2.

Table 2.

PSG indicators before and after 3 months of melatonin therapy

Variable	Before melatonin therapy	P-value	After melatonin therapy
Total study time, min	450.3±32.3	>0.05	432.5±21.5
Total sleep time, min	318.5±19.5	<0.05	413.9±12.1
Sleep latency	39.45±6.71	<0.05	23.25±3.71
Overall sleep efficiency, %	70.74±9.43	<0.05	95.7±5.09
WASO, min	41.57±6.22	>0.05	36.2±4.8
SWS Stages 1 and 2, min	177.9±64.21	>0.05	189.22±16.78
SWS Stage 3, min	91.92±36.62	>0.05	113.77±33.25
REMS, min	94.72±21.77	<0.05	135.63±22.76
EEG activation reactions, n	34.2±6.7	<0.05	24.2±7.1
AHI, e/h	3.31±2.74	>0.05	4.36±3.45
SaO_2, %	98.16±0.94	>0.05	97.23±1.6

PSG demonstrated improvement in sleep latency, overall sleep efficiency, and an increase of REM sleep. A statistically significant number of EEG activation reactions indicate a decrease in sleep fragmentation and an improvement in sleep segmental structure. The observed tendency toward a decrease in wakefulness time during sleep is not statistically significant; this tendency is associated with the preservation of nocturnal awakenings, although their number decreased to one episode in patients with complaints of 2 or more episodes of awakenings. The tendency toward an increase in superficial sleep can be explained by an increase in the total sleep time in patients taking melatonin. A slight increase in AHI was detected, although these indicators are within the reference values, which, quite possibly, is explained by a more general relaxation of smooth muscles due to an increase in the total duration of REM sleep. The current PSG study showed an improvement of some sleep parameters in perimenopausal women with insomnia after melatonin intake in a dose of 3mg/day for 3 months.

Discussion

Our results are consistent with the previously described effects of the use of melatonin drugs in the treatment of SDs. The efficacy of melatonin administration in patients with chronic cerebral insufficiency with SDs has been shown quite convincingly during a multicenter open observational non-comparable study of its effectiveness and safety.[11] However, this large-scale study evaluated only the subjective characteristics of sleep. It should be noted that the use of melatonin as an adaptogen that significantly improves the quality of life in monotherapy for menopausal disorders and premenstrual syndrome has been found previously.[16] Our results are in good agreement with the results of other researchers,[17] who found a decrease in latency to sleep and a decrease in microactivation with the use of melatonin. Our study also demonstrates a change in the structure of sleep. Analyzing the results obtained, it should be noted that there is an increase in the presence of REM sleep after melatonin use, which is the main factor in improving quality of sleep and, accordingly, normalizing the “sleep-wake” continuum. It can be considered that an increase in the presence of REM sleep is one of the manifestations of the compensatory-adaptive reaction of the sleep homeostasis system. These findings are consistent with the conclusions about the role of REM in human mental life.[18-20] However, we believe that the effect of taking melatonin-based drugs is based not only on their chronobiological effect, but also on their antioxidant potential ability to correct pro-oxidant/antioxidant discoordination, and increasing free radical lipid oxidation due to estrogen deficiency.[21]

Summarizing all the above, relying on our own data and the research results of other authors, it can be stated that the use of melatonin in a dose of 3mg/day for 3 months is one of the main methods for treatment of SDs in age-related estrogen-deficient situations. The main clinical effect, which significantly improves the quality of life, is associated with the elimination of pre- and intrasomnic disorders. We agree with

the authors[12] that melatonin acts as a systemic adaptogen in the disorders of the female reproductive system.

However, it is of great interest to change the structure of sleep by the combined therapy of melatonin and menopausal hormonal drugs in more severe manifestations of insomnia disorders with a tendency toward an increase in systemic disorders associated with estrogen and melatonin deficiency. However, it will be the goal of further scientific research.

Competing Interests

The authors declare that they have no competing interests.

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