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Evaluation of Exogenous Melatonin Administration in Improvement of Sleep Quality in Patients with Chronic Obstructive Pulmonary Disease

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Background: COPD is primarily the disease of the lungs; nevertheless, multiple systemic manifestations including poor sleep quality and sleep disturbances have been linked to this illness. Administration of sedative hypnotics is not recommended in COPD patients, as these drugs suppress the ventilatory response and exacerbate sleep-related disorders. Melatonin is an alternative medication that has been widely used to treat sleep disturbances caused by aging and other specific conditions. We aimed to investigate the efficacy of melatonin administration in improvement of sleep quality in COPD patients.

Materials and Methods: A randomized, double-blind, placebo-controlled trial was conducted. A total of 54 patients were recruited and randomly assigned into either melatonin or placebo group. Sleep quality was evaluated by Pittsburgh Sleep Quality Index (PSQI); daytime sleepiness was assessed by Epworth Sleepiness Scale (ESS). For all patients, spirometry and pulse oximetry were preformed to evaluate lung function and oxygenation.

Results: Compared with placebo, melatonin administration significantly improved global PSQI score ($p<0.001$). Of PSQI individual components, sleep quality ($p=0.001$), sleep latency ($p=0.001$), sleep efficacy ($p=0.003$), and sleep duration ($p=0.024$) improved significantly. On the other hand, melatonin treatment did not significantly change indices of daytime sleepiness, lung function and oxygenation ($p>0.05$).

Conclusion: Melatonin significantly improves sleep quality in COPD patients with sleep complaints. This improvement was in the absence of significant elevation in the indices of daytime sleepiness and lung function.

Key words: Melatonin, Sleep quality, Chronic obstructive pulmonary disease

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a progressive condition characterized by irreversible limitation of airflow (1). COPD imposes a significant burden; in 2000, the World Health Organization (WHO) estimated that 2.47 million people died from COPD worldwide. It is projected that by 2020, COPD will become the third leading cause of death (2). In the United Kingdom, COPD is the leading cause of chronic respiratory disease (3). The main risk factor for developing COPD is smoking; others include air pollution, occupational

exposure to chemical substances and dusts, poor nutritional status, alcohol consumption and alpha-1-antitrypsin deficiency (4).

COPD primarily affects the lungs; however, various systemic complications including pulmonary hypertension (5,6), cor pulmonale (7,8), weight loss (9,10), insulin resistance (11), systemic inflammation (12), depression (13,14), and sleep disturbances (15) have been linked to COPD.

An important and common systemic consequence of COPD is sleep disturbances characterized by insomnia and poor sleep quality. A rich body of subjective and objective evidence exist describing sleep disturbances in COPD patients (16-19). Sleep disorders and insomnia negatively affect the quality of life of COPD patients (20). Administration of conventional sedative-hypnotic drugs (e.g. benzodiazepines) is not recommended in patients with respiratory failure, as these drugs may suppress ventilatory response and exacerbate sleep-related breathing disorders (21).

Melatonin, an endogenous hormone synthesized and secreted into the systemic circulation and cerebrospinal fluid by the pineal gland (22), is believed to play a cardinal role in regulating the circadian rhythm and sleeping during the night. Melatonin has been widely used to treat sleep disturbances and insomnias caused by aging and other specific pathologic conditions (23-25).

Given the principal role of melatonin in regulation of somnolence, we aimed to evaluate the efficacy of exogenous melatonin administration in improving sleep quality in COPD patients.

MATERIALS AND METHODS

In order to evaluate the effect of melatonin therapy on sleep quality of COPD patients, a randomized, double-blind, placebo controlled clinical trial was conducted in Respiratory Department of Shahid Sadoughi Hospital, Yazd, Iran. All patients had a stable condition and complained of sleep disorder. The exclusion criteria were as follows: (1) history of COPD exacerbation in the past month (2) presence of obstructive sleep apnea (3) history of mental disorders known to affect sleep (e.g. anxiety and depression spectrum) (4) prior use of sedative-hypnotic drugs (5) use of nocturnal oxygen therapy.

Fifty-four patients with confirmed diagnosis of stage II to IV COPD based on Global Initiative for Chronic Obstructive Disease (GLOD) criteria (26) were initially recruited in this study and were randomly assigned into two groups (melatonin and placebo). Forty-eight patients completed the study protocol. For patients in melatonin group, 3 mg melatonin was prescribed one hour before bedtime and the other group received placebo.

Primary outcome was quality of night sleep evaluated by Pittsburgh Sleep Quality Index (PSQI). The PSQI is a composite score constituting of seven components: 1) subjective sleep quality 2) sleep latency 3) sleep duration 4) sleep efficacy 5) sleep disturbance 6) use of sleep medication 7) and daytime dysfunction due to inadequate night sleep. Each component has a 0-3 scale with a total score of 0-21. A total PSQI score of greater than 5 manifests poor sleep quality with a sensitivity of 89.6% and specificity of 86.5% (27). Since patients with the history of sedative-hypnotic medication use were excluded from the study, score of the sixth component was set as zero for all patients.

Secondary outcomes were daytime sleepiness and lung function and oxygenation. Daytime sleepiness was evaluated by Epworth Sleepiness Scale (ESS), a subjective questionnaire designed to determine the level of daytime sleepiness. Patients are asked to rate the probability of sleeping or dozing on a scale of increasing probability from 0 (none) to 3 (high probability) for eight different situations (sitting and reading, watching TV, sitting inactive in a public place, being a passenger in a vehicle for an hour

without a break, lying down to rest in the afternoon whenever circumstances permit, sitting and talking to someone, Sitting quietly after a lunch without alcohol, sitting in a vehicle while stopped in traffic for a few minutes). Individual scores gained from these eight sections are then summed to produce a composite score. A total score of 10 or more is considered as excessive daytime sleepiness (28).

Lung function and oxygenation were assessed by means of spirometry and pulse oximeter (Spirolab III , MIR company, Italy) and for each patient FEV1, FVC, FEV1/FVC, FEF 25-75 and O_2 saturation were calculated. After one month, evaluation of sleep quality, daytime sleepiness and lung function was repeated for all patients. Statistical analyses were performed using SPSS version 17.0 software for windows (SPSS Inc. Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation. Categorical variables (i.e. gender and smoking status) were presented as percentage. Independent t-test was employed to compare baseline measurements of continuous variables between melatonin and placebo groups. The efficacy of treatment modality within each group was assessed using paired t-test. To compare the effects of melatonin versus placebo after one month, analysis of variance (ANOVA) was conducted. In all tests, a p-value of less than 0.05 was considered statistically significant.

RESULTS

A randomized double blind, placebo-controlled trial was conducted to assess the efficacy of melatonin administration in improving sleep quality in COPD patients. Initially, a total of 54 consecutive patients with stage II to IV COPD were enrolled and randomly assigned into either melatonin or placebo group. Six patients were excluded from the study; two patients from melatonin group experienced COPD exacerbation, four patients did not return for a follow up visit (two patients from each group). At the end of trial, 48 patients completed the protocol (23 from the melatonin group and 25 from the placebo group). There were no significant side effects in the two groups.

The mean age of the study participants was 66.32 ± 9.5 yrs. (range 46 to 83). Forty (83.3%) patients were men and 8 (16.7%) were women. Twenty-nine (60.4%) patients had a history of smoking.

Prior to treatment, there were no significant differences between the two groups in global PSQI scores, ESS scores, age, body mass index (Table 1) and spirometry and oxygenation indices (Table 3).

Table 2 present PSQI global and sub domains score for study groups prior and after treatment. Global PSQI scores significantly improved in melatonin group after treatment ($p=0.002$). Comparing cases and controls, melatonin was superior to placebo in improving global PSQI score ($p<0.001$). Among PSQI individual components, sleep quality ($p=0.001$), sleep latency ($p=0.001$), sleep efficacy ($p=0.003$), and sleep duration ($p=0.024$) improved significantly in cases after melatonin administration. On the other hand, melatonin treatment did not significantly change indices of daytime sleepiness, lung function or oxygen saturation ($p>0.05$). Spirometry indices and oxygen saturation before and after treatment are presented in Table 3.

Table 1. Baseline characteristics of the melatonin and placebo groups

	Melatonin	Placebo	P value
Age	65.7±9.34	66.85±9.62	0.658
BMI	23.62±4.48	24.87±4.72	0.323
PSQI	11.63±3.96	10.66±2.48	0.206
ESS	7.04±4.43	6.33±3.5	0.530

BMI, body mass index; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale.

Table 2. PSQI (individual components and global score) before and after treatment in melatonin and placebo groups

		Melatonin	Placebo	P value[a]	P value[b]
Sleep quality	Before	2±0.95	1.89±0.57	0.490	
	After	1.52±0.84	1.77±0.57		
	P value[c]	0.001	0.18		
Sleep latency	Before	2.22±0.95	2.04±0.89	0.494	
	After	1.74±1.17	1.74±0.86		
	P value	0.001	0.23		
Sleep duration	Before	2.48±0.89	2.22±0.69	0.056	
	After	1.70±1.02	2.14±0.76		
	P value	0.024	0.41		
Sleep efficacy	Before	2.30±1.06	2.11±1.05	0.522	
	After	1.61±1.27	2.03±1.12		
	P value	0.003	0.15		
Sleep disturbance	Before	1.65±0.83	1.74±0.66	0.634	
	After	1.55±0.65	1.7±0.66		
	P value	0.080	0.31		
Use of sleep medicine	Before	0	0	n/a	
	After	0	0		
	P value	0	0		
Daytime dysfunction	Before	0.91±0.85	0.63±0.84	0.178	
	After	0.78±0.67	0.7±0.91		
	P value	0.180	0.157		
Global Score	Before	11.63±3.96	10.66±2.48	0.206	
	After	8.7±4.15	10.11±2.66		<0.001
	P value	0.002	0.065		

a. P value calculated for comparison of baseline differences between melatonin and placebo groups

b. P value calculated for comparison of treatment efficacy between melatonin and placebo groups

c. P value calculated for within group comparison (before and after treatment)

Abbreviations: PSQI, Pittsburgh Sleep Quality Index; n/a, not applicable

Table3. Spirometry indices and oxygen saturation before and after treatment in melatonin and placebo groups

		Melatonin	Placebo	P value[a]	P value[b]
FEV1/FVC	Before	66.35 ± 6.31	62.67 ± 7.97	0.080	
	After	66.47 ± 6.46	63.04 ± 6.85		0.273
	P value[c]	0.633	0.607		
FEV1 (%)	Before	47.04 ± 14.68	45.26 ± 14.81	0.672	
	After	47.52 ± 14.83	45.54 ± 15.17		0.729
	P value	0.077	0.423		
FVC (%)	Before	50.35 ± 14.01	48.74 ± 15.18	0.701	
	After	50.30 ± 14.43	48.92 ± 15.49		0.841
	P value	0.911	0.672		
FEF 25-75%	Before	38.65 ± 17.02	35.52 ± 16.76	0.516	
	After	38.80 ± 16.96	36.48 ± 16.70		0.691
	P value	0.426	0.081		
O_2 saturation (%)	Before	91.52 ± 3.61	91.00 ± 3.44	0.607	
	After	91.91 ± 3.89	91.26 ± 2.82		0.423
	P value	0.131	0.336		

a. P value calculated for comparison of baseline differences between melatonin and placebo groups

b. P value calculated for comparison of treatment efficacy between melatonin and placebo groups

c. P value calculated for within group comparison (before and after treatment)

FEV1, forced expiratory volume at the end of first second; FVC, forced vital capacity; FEF, forced expiratory flow

DISCUSSION

In this study 48 patients with stage II to IV COPD were investigated in a randomized clinical trial to reveal the effect of melatonin administration on sleep quality. Our results corroborate the results of previous studies. Shilo et al, (29) for the first time evaluated the effects of melatonin on improvement of sleep quality in COPD patients. They studied eight patients in pulmonary ICU with exacerbation of COPD; sleep quality was assessed using wrist actinography. They observed a significant improvement in sleep quality and sleep duration after melatonin treatment. They recommended melatonin administration for sleep induction and resynchronization of biological clock in ICU patients. In contrast to Shilo et al, our study participants were in ambulatory condition and had not experienced exacerbation episodes at least in the past month. Thus, melatonin has beneficial effects on both outpatients and inpatients. Nunes et al. (30) also used melatonin administration to resolve sleep disturbances in COPD patients. Similar to our study, PSQI was used to evaluate sleep quality. Additionally, daytime sleepiness, pulmonary function and functional exercise level were measured using ESS, spirometry and the 6-minute walk test, respectively. After melatonin prescription, global PSQI scores significantly improved compared with the placebo group. However, no significant differences were observed in other variables. Nunes et al. used melatonin in all COPD patients but we used this drug in COPD patients with sleep disturbances (PSQI >5). Melatonin is administered to treat poor sleep quality; therefore, selection of these patients is reasonable. Also Nunes et al. (30) showed that melatonin had no effect on sleep latency but in our study sleep latency decreased clearly. Thus, it seems that melatonin consumption could accelerate the onset of sleep. In another study by Campos et al. (31) effects of melatonin administration on improvement of sleep quality and pulmonary function in asthma patients were investigated. They concluded that melatonin significantly improved sleep quality but had no significant effects on peak flow and asthma symptoms. In our study melatonin had no sizeable effects on spirometry parameters such as FEV1, FVC, FEV1/FVC and FEF 25-75.

As stated earlier, melatonin has long been used for treatment of certain insomnia and regulation of circadian rhythm sleep disorders (CRSDs) (32). For instance, Zhdanova et al. in a series of studies revealed that melatonin administration in healthy individuals reduces sleep latency and results in improved sleep efficacy (33,34). Melatonin levels drop with advanced age (35,36), and it has been hypothesized that this decrement is a principal cause for poor sleep quality and sleep disturbance in the elderly. Garfinkel et al. (37) demonstrated that melatonin administration improves sleep efficiency in the elderly population. Moreover, a number of brain pathologies, such as Alzheimer's disease are associated with decrease in melatonin levels and resultant sleep disturbances; beneficial effects of exogenous melatonin on these patients have been proven in different studies (38-40). Safety issues in melatonin administration have also been thoroughly assessed. A recent meta-analysis showed the safety of short-term administration of melatonin (41). Our observations confirmed the previous results and no major side effects were reported in patients receiving melatonin.

Mechanisms by which melatonin exerts its main effects remain largely unknown. Recent evidence indicates that melatonin, when secreted in its physiological dose, is able to interrupt circadian rhythm that maintains insomnolence via a receptor-mediated pathway (22).

In conclusion, wide range of therapeutic use of melatonin in treatment of sleep disturbances reveals the efficacy of this agent and the potential use of melatonin for improving sleep quality in COPD patients with sleep complaints.

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REFERENCES

1. Pauwels RA, Rabe KF. Burden and clinical features of chronic obstructive pulmonary disease (COPD). *Lancet* 2004; 364 (9434): 613- 20.
2. Singh S. Chronic obstructive pulmonary disease. *Current Anaesthesia & Critical Care* 2003; 14(2): 74-80.
3. Raherison C, Girodet PO. Epidemiology of COPD. *Eur Respir Rev* 2009; 18 (114): 213- 21.
4. Viegi G, Scognamiglio A, Baldacci S, Pistelli F, Carrozzi L. Epidemiology of chronic obstructive pulmonary disease (COPD). *Respiration* 2001; 68 (1): 4- 19.
5. Barberà JA, Peinado VI, Santos S. Pulmonary hypertension in chronic obstructive pulmonary disease. *Eur Respir J* 2003; 21 (5): 892- 905.
6. Kessler R, Faller M, Weitzenblum E, Chaouat A, Aykut A, Ducoloné A, et al. "Natural history" of pulmonary hypertension in a series of 131 patients with chronic obstructive lung disease. *Am J Respir Crit Care Med* 2001; 164 (2): 219- 24.
7. Vonk-Noordegraaf A, Marcus JT, Holverda S, Roseboom B, Postmus PE. Early changes of cardiac structure and function in COPD patients with mild hypoxemia. *Chest* 2005; 127 (6): 1898- 903.
8. Weitzenblum E. Chronic cor pulmonale. *Heart* 2003; 89 (2): 225- 30.
9. Schols AM, Slangen J, Volovics L, Wouters EF. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 157 (6 Pt 1): 1791- 7.
10. Landbo C, Prescott E, Lange P, Vestbo J, Almdal TP. Prognostic value of nutritional status in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 160 (6): 1856- 61.
11. Bolton CE, Evans M, Ionescu AA, Edwards SM, Morris RH, Dunseath G, Luzio SD, et al. Insulin resistance and inflammation - A further systemic complication of COPD. *COPD* 2007; 4 (2): 121- 6.
12. Gan WQ, Man SF, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. *Thorax* 2004; 59 (7): 574- 80.
13. Maurer J, Rebbapragada V, Borson S, Goldstein R, Kunik ME, Yohannes AM, et al. Anxiety and depression in COPD: current understanding, unanswered questions, and research needs. *Chest* 2008; 134 (4 Suppl): 43S- 56S.
14. Lee H, Kim I, Lim Y, Jung HY, Park HK. Depression and sleep disturbance in patients with chronic obstructive pulmonary disease. *Geriatr Nurs* 2011; 32 (6): 408- 17.
15. Vallarino C, Rajagopalan R, Mini L. Prevalence of insomnia among patients with chronic obstructive pulmonary disease in a large database. *Value in Health* 2005; 8(3): 322.
16. Leitch AG, Clancy LJ, Leggett RJ, Tweeddale P, Dawson P, Evans JI. Arterial blood gas tensions, hydrogen ion, and electroencephalogram during sleep in patients with chronic ventilatory failure. *Thorax* 1976; 31 (6): 730- 5.
17. Calverley PM, Brezinova V, Douglas NJ, Catterall JR, Flenley DC. The effect of oxygenation on sleep quality in chronic bronchitis and emphysema. *Am Rev Respir Dis* 1982; 126 (2): 206- 10.
18. Arand DL, McGinty DJ, Littner MR. Respiratory patterns associated with hemoglobin desaturation during sleep in chronic obstructive pulmonary disease. *Chest* 1981; 80 (2): 183- 90.
19. Fleetham J, West P, Mezon B, Conway W, Roth T, Kryger M. Sleep, arousals, and oxygen desaturation in chronic obstructive pulmonary disease. The effect of oxygen therapy. *Am Rev Respir Dis* 1982; 126 (3): 429- 33.
20. Kyle SD, Morgan K, Espie CA. Insomnia and health-related quality of life. *Sleep Med Rev* 2010; 14 (1): 69- 82.
21. Guilleminault C. Benzodiazepines, breathing, and sleep. *Am J Med* 1990; 88 (3A): 25S- 28S.
22. Blask DE. Melatonin, sleep disturbance and cancer risk. *Sleep Med Rev* 2009; 13 (4): 257- 64.
23. Brzezinski A, Vangel MG, Wurtman RJ, Norrie G, Zhdanova I, Ben-Shushan A, et al. Effects of exogenous melatonin on sleep: a meta-analysis. *Sleep Med Rev* 2005; 9 (1): 41- 50.
24. Dahlitz M, Alvarez B, Vignau J, English J, Arendt J, Parkes JD. Delayed sleep phase syndrome response to melatonin. *Lancet* 1991; 337 (8750): 1121- 4.
25. Shamir E, Laudon M, Barak Y, Anis Y, Rotenberg V, Elizur A, et al. Melatonin improves sleep quality of patients with chronic schizophrenia. *J Clin Psychiatry* 2000; 61 (5): 373- 7.

26. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007; 176 (6): 532- 55.
27. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989; 28 (2): 193- 213.
28. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991; 14 (6): 540- 5.
29. Shilo L, Dagan Y, Smorjik Y, Weinberg U, Dolev S, Komptel B, et al. Effect of melatonin on sleep quality of COPD intensive care patients: a pilot study. *Chronobiol Int* 2000; 17 (1): 71- 6.
30. Nunes DM, Mota RM, Machado MO, Pereira ED, Bruin VM, Bruin PF. Effect of melatonin administration on subjective sleep quality in chronic obstructive pulmonary disease. *Braz J Med Biol Res* 2008; 41 (10): 926- 31.
31. Campos FL, da Silva-Júnior FP, de Bruin VM, de Bruin PF. Melatonin improves sleep in asthma: a randomized, double-blind, placebo-controlled study. *Am J Respir Crit Care Med* 2004; 170 (9): 947- 51.
32. Turek FW, Gillette MU. Melatonin, sleep, and circadian rhythms: rationale for development of specific melatonin agonists. *Sleep Med* 2004; 5 (6): 523- 32.
33. Zhdanova IV, Wurtman RJ, Lynch HJ, Ives JR, Dollins AB, Morabito C, et al. Sleep-inducing effects of low doses of melatonin ingested in the evening. *Clin Pharmacol Ther* 1995; 57 (5): 552- 8.
34. Zhdanova IV, Wurtman RJ, Morabito C, Piotrovska VR, Lynch HJ. Effects of low oral doses of melatonin, given 2-4 hours before habitual bedtime, on sleep in normal young humans. *Sleep* 1996; 19 (5): 423- 31.
35. Waldhauser F, Weiszenbacher G, Tatzer E, Gisinger B, Waldhauser M, Schemper M, et al. Alterations in nocturnal serum melatonin levels in humans with growth and aging. *J Clin Endocrinol Metab* 1988; 66 (3): 648- 52.
36. Sharma M, Palacios-Bois J, Schwartz G, Iskandar H, Thakur M, Quirion R, et al. Circadian rhythms of melatonin and cortisol in aging. *Biol Psychiatry* 1989; 25 (3): 305- 19.
37. Garfinkel D, Laudon M, Nof D, Zisapel N. Improvement of sleep quality in elderly people by controlled-release melatonin. *Lancet* 1995; 346 (8974): 541- 4.
38. Brusco LI, Márquez M, Cardinali DP. Monozygotic twins with Alzheimer's disease treated with melatonin: Case report. *J Pineal Res* 1998; 25 (4): 260- 3.
39. Brusco LI, Fainstein I, Márquez M, Cardinali DP. Effect of melatonin in selected populations of sleep-disturbed patients. *Biol Signals Recept* 1999; 8 (1-2): 126- 31.
40. Cohen-Mansfield J, Garfinkel D, Lipson S. Melatonin for treatment of sundowning in elderly persons with dementia - a preliminary study. *Arch Gerontol Geriatr* 2000; 31 (1): 65- 76.
41. Buscemi N, Vandermeer B, Hooton N, Pandya R, Tjosvold L, Hartling L, et al. Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis. *BMJ* 2006; 332 (7538): 385- 93.