DOI: *http://dx.doi.org/10.18502/cjn.v23i1.???*

Current Journal of Neurology

Original Paper

Curr J Neurol 2024; 23(1): 39-43

Podcast

Comparison of the effectiveness of modafinil and methylphenidate in treatment of excessive daytime sleepiness in patients with Parkinson's disease

Received: 07 Sep. 2023
Accepted: 03 Nov. 2023

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Keywords
Parkinson Disease; Excessive Daytime Sleepiness; Sleep Quality; Modafinil; Methylphenidate

Abstract

Background: A large percentage of patients with Parkinson's disease (PD) suffer from excessive daytime sleepiness (EDS). This study aims to compare the effectiveness of modafinil and methylphenidate on EDS and side effects.

Methods: Fifty nine patients with PD and EDS [Epworth Sleepiness Scale (ESS) more than 9] were recruited in a double-blind placebo controlled trial. Twenty-two patients received modafinil 200 mg daily, twenty-six patients received methylphenidate 10 mg daily, and 11 patients received placebo for 6 weeks. Pittsburgh Sleep Quality Index (PSQI) and ESS were filled out at baseline and 6 weeks later.

Results: There was no significant difference in demographics, PSQI, and ESS variables at baseline. The mean of ESS scores decreased significantly in modafinil (17.36 ± 5.05 vs. 10.55 ± 4.62, P < 0.001) and methylphenidate (16.27 ± 5.40 vs. 12.23 ± 6.28, P < 0.001) groups after 6-week trial, compared with control group (14.27 ± 4.49 vs. 14.09 ± 4.46, P = 0.710). The effectiveness of modafinil and methylphenidate on improving daytime sleepiness and night sleep of patients was not significantly different.

How to cite this article: Chitsaz A, Najafi MR, Habibi F, Amirhajloo S. Comparison of the effectiveness of modafinil and methylphenidate in treatment of excessive daytime sleepiness in patients with Parkinson's disease. Curr J Neurol 2024; 23(1): 39-43.

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Conclusion: Both modafinil and methylphenidate were effective drugs in improving EDS and quality of sleep without significant difference in efficiency and side effects.

Introduction

Parkinson's disease (PD) is the most common degenerative disease with motor manifestations in the world, and the most common neurodegenerative disease after Alzheimer's.[1] It is one of the most important reasons of disability especially in developed and aged countries. Attention has been made recently about non-motor manifestations of PD, like excessive daytime sleepiness (EDS).[1]

EDS is defined as disability to maintain alertness and awareness in main periods of wakefulness during day which causes unwanted somnolence and sleep.[2] EDS is reported in 21%-76% of patients with PD, which is significantly higher than general population.[3-5] EDS disturbs quality of life, increases disease burden, and destroys night sleep quality.[6]

Various articles reported positive impacts of modafinil on EDS in patients with narcolepsy, obstructive sleep apnea (OSA), and shift work-related sleep disorders, as well as patients with PD.[1,7-12] Positive experience exists about methylphenidate in treating EDS and narcolepsy in Parkinson and non-Parkinson's patients.[9,10,13-19] We designed a double-blind placebo controlled trial to compare the efficacy of modafinil and methylphenidate in patients with PD.

Materials and Methods

Patients and settings: Ethical Committee of Isfahan University of Medical Sciences, Isfahan, Iran, approved this clinical trial (IR.MUI.MED.REC.1401.030) and the protocol of this study was registered in Iranian Registry of Clinical Trials (IRCT20220623055257N1). We conducted a double-blind placebo controlled trial. Patients with PD, presenting to Alzahra and Kashani Clinics in Isfahan City, complaining of EDS [Epworth Sleepiness Scale (ESS) equal to and more than 10], were recruited. Exclusion criteria were as follows: using of sedative drugs, suffering from depression or other psychological disorder, thyroid problems, liver, kidney, or pulmonary dysfunction, having shift works, allergy to modafinil or methylphenidate, and using apomorphine. The patients were randomly divided into three groups. The first group received placebo, the second group was treated with modafinil (200 mg daily in the morning), and the third group was treated with methylphenidate (10 mg daily in the morning) for 6 weeks. They filled out demographic, ESS, and Pittsburgh Sleep Quality Index (PSQI) questionnaires at baseline and then 6 weeks later. All patients were monitored closely during the trial and all complications were recorded.

ESS: ESS is a short questionnaire asking about daily drowsiness during activities such as sitting and reading books, watching TV, sitting in a public place without movement and special activities as a traveler. It has 8 questions which score 0-3, with whole questionnaire scoring 0-24. Scores equal and more than 10 were supposed as daily sleepiness.

PSQI: PSQI questionnaire assesses sleep quality using 19 questions and 7 components; each component scores 0-3, and the whole questionnaire scores 0-21. Higher scores show poorer sleep quality. Scores equal to or more than 5 are defined as poor sleep quality.

The data were analyzed using SPSS software (version 28, IBM Corporation, Armonk, NY, USA). Descriptive data are presented as number (percent) and mean ± standard deviation (SD). One-way analysis of variance (ANOVA), chi-square test, independent t-test, and Wilcoxon test were used to assess difference between groups before and after intervention.

Results

Fifty nine patients successfully completed our study. Table 1 presents baseline demographic characteristics. There was no significant difference among groups in demographic and baseline variables such as ESS and PSQI scores. Figure 1 illustrates ESS before and after 6 weeks of intervention.

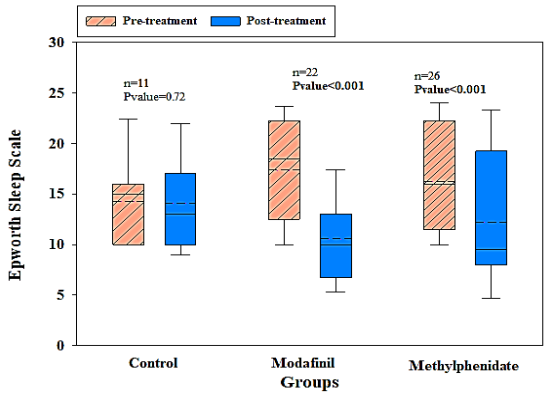

Figure 1. Changing Epworth Sleepiness Scale (ESS) before and after intervention based on groups

Table 1. Baseline demographic variables of study between groups

Variables	Control (n = 11)	Modafinil (n = 22)	Methylphenidate (n = 26)	P
Age (year) (mean ± SD)	71.45 ± 9.82	65.68 ± 9.61	66.96 ± 8.12	0.22*
Gender (male) [n (%)]	9 (81.8)	14 (63.6)	19 (73.0)	0.53**
Marital status (married) [n (%)]	10 (90.9)	19 (86.3)	20 (76.9)	0.51**
Education (n)				0.51**
Illiterate	1	3	9	
Elementary	2	6	8	
Junior high school	2	4	2	
Diploma and bachelor's	5	5	5	
Post graduate	1	1	1	
Retirement (yes) [n (%)]	10 (90.9)	16 (95.4)	21 (80.7)	0.47**
Smoker (no) [n (%)]	10 (90.9)	21 (95.4)	24 (92.3)	0.86**
Duration of disease (year) (mean ± SD)	8.00 ± 4.66	4.90 ± 4.80	6.22 ± 6.50	0.36*
BMI (kg/m^2) (mean ± SD)	20.88 ± 5.32	25.63 ± 3.81	27.58 ± 4.59	0.35*
Medication (n)				0.60**
Levodopa	4	9	6	
Levodopa + dopamine agonist	0	2	3	
Levodopa + amantadine	3	8	10	
Levodopa + dopamine agonist + amantadine	4	3	7	

*One-way analysis of variance (ANOVA); **Chi-square test
P-value less than 0.05 was considered statistically significant
SD: Standard deviation; BMI: Body mass index

Subjects on modafinil and methylphenidate groups showed significant improvement compared with placebo group (P < 0.001). Furthermore, figure 2 illustrates sleep quality before and after intervention. Subjects on modafinil and methylphenidate groups showed significant improvement in PSQI scores compared with placebo group (P = 0.001 and P = 0.020, respectively). Table 2 presents mean comparison test of modafinil and methylphenidate effectiveness plus the comparison of these agents' side effects. The effectiveness of modafinil and methylphenidate on improving daytime sleepiness and night sleep of patients was not significantly different.

Generally, our patients tolerated the drug well. Some minor adverse effects were reported.

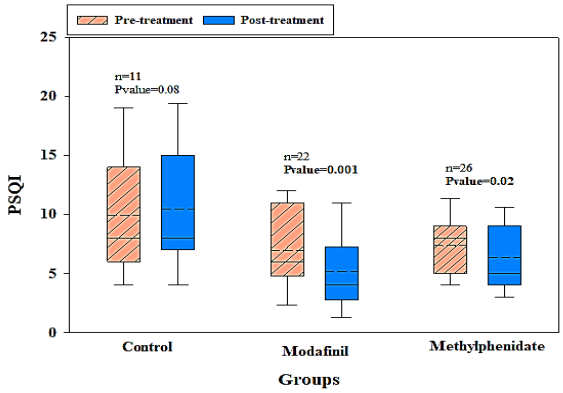

Figure 2. Changing Pittsburgh Sleep Quality Index (PSQI) before and after intervention based on groups

Table 2. Comparison of modafinil and methylphenidate effectiveness

Variables	Control (n = 11)	Modafinil (n = 22)	Methylphenidate (n = 26)	P
ESS (mean ± SD)				
Before	14.27 ± 4.49^a	17.36 ± 5.05^a	16.27 ± 5.40^a	0.260#
After	14.09 ± 4.46^a	10.55 ± 4.62^a	12.23 ± 6.28^a	0.150#
P	0.720¥	< 0.001¥	< 0.001¥	
PSQI (mean ± SD)				
Before	9.91 ± 5.00^a	6.95 ± 3.82^a	7.35 ± 2.78^a	0.220#
After	10.45 ± 5.29^a	5.14 ± 3.31^b	6.35 ± 3.34^b	0.008#
P	0.080¥	0.001¥	0.020¥	
Side effect [n (%)]	1 (9.0)	2 (9.0)	3 (11.0)	0.954#

#Nonparametric test (independent samples Kruskal-Wallis test); ¥Nonparametric test (Wilcoxon test)
Values followed by different letters within a row are significantly different at 5% level.
ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index; SD: Standard deviation

In control group, one patient complained of headache (9% of patients in control group). In modafinil group, one complained of headache and one of nausea (9% of patients in modafinil group). In methylphenidate group, one complained of bruxism, one of exacerbating tremor, and one of insomnia (11% of patients in methylphenidate group). All adverse effects were minimal, did not require special treatment, and resolved with reassurance in less than 1 week. Methylphenidate and modafinil groups were not significantly different in terms of incidence and severity of side effects.

Discussion

Our study aimed to compare the effectiveness of modafinil and methylphenidate on daytime sleepiness and quality of sleep in patients with PD. Few studies compared these two drugs' efficacy, especially in patients with PD. In Black et al.'s study, modafinil was effective and also had minor side effects in treatment of EDS in patients with narcolepsy.[20] Nieves and Lang showed the possible effectiveness of modafinil in treatment of EDS in patients with PD. It did not exacerbate the PD symptoms; furthermore, it allowed for increasing the dosage of dopamine agonists which was limited by EDS.[8] Rodrigues et al.'s meta-analysis reported that modafinil effectively reduced ESS score, within overall mean difference of 2.2 [95% confidence interval (CI): -3.9 to -0.6].[21] In a murine experimental model, modafinil improved levodopa-induced excessive nighttime sleepiness and increased noradrenaline concentration in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mice.[22]

Methylphenidate is a drug used for treating attention-deficit/hyperactivity disorder (ADHD), narcolepsy through stimulating central nervous system (CNS).[15] Banerjee et al. showed methylphenidate as an effective drug for treating EDS with acceptable side effects.[13] Bosco et al. reported positive impacts for methylphenidate treating narcolepsy although it may increase patients' blood pressure after long-term usage.[23] Methylphenidate also improved EDS in patients with PD. Devos et al. reported improvement of EDS, motor, and gait symptoms with high dose and chronic usage of methylphenidate.[16] Sheikhinia et al. compared modafinil and methylphenidate in intractable epilepsy; both drugs effectively decreased EDS and total sleep time, without significant difference in side effects.[9] Switching from methylphenidate to modafinil without washout period or with methylphenidate tapering was successful and also effective in decreasing EDS.[10]

Modafinil demonstrated no significant change on objective variables of sleep, but healthy volunteers reported better sleep quality on subjective assessment.[24] Sodium oxybate improved subjective sleep quality with or without modafinil in patients with narcolepsy. Modafinil alone did not have such an effect.[7] sleep objective assessment showed no difference in patients with narcolepsy who took modafinil compared with placebo.[12] Methylphenidate caused later sleep onset and shorter sleep duration, but lower and shorter periods of interruptions leading to more consolidated sleep in ADHD cases.[14] In a trial with methylphenidate in patients with ADHD, sleep efficiency in polysomnography (PSG) improved and better feeling about sleep quality was reported.[19]

Various studies investigated modafinil and methylphenidate side effects in different age groups with different underlying diseases. In therapeutic doses, minor side effects occurred.[5,8,9,13,15-20] Our study showed the positive effect of modafinil and methylphenidate on daytime sleepiness scores and sleep quality.

Conclusion

There was no significant difference between modafinil and methylphenidate groups regarding the effectiveness and side effects. Both drugs can be safely used without preference by physicians in old patients with PD who are fragile cases for using these agents. More studies with objective methods, a larger study population, and investigating other aspects of drug effect such as mood, cognition, and motor symptoms of patients with PD can show more reliable results.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

This study was funded by Isfahan University of Medical Sciences. We want to thank all the participants of this research.

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