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Research Article

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The Effect of Pramipexole Combined with rTMS on Sleep Disorders in Parkinson's Disease Patients

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Abstract

Background: Sleeping disorder is a debilitating condition of non-motor symptoms in patients with Parkinson's disease (PD). Pramipexole could improve sleep disorders in PD patients, while repetitive transcranial magnetic stimulation (rTMS) also improves sleep in PD. However, there is no report on whether a combination therapy of Pramipexole with rTMS would produce a better therapeutic effect over administration of Pramipexole alone.

Objective: To evaluate the clinical effect of pramipexole combined with rTMS on sleep disorders in PD patients.

Methods: PD patients with sleep disorders were selected and divided into the control group and the treatment group using a random number table method. The control group was treated with pramipexole (0.25 mg tid), and the treatment group was treated with both pramipexole (0.25 mg tid) and rTMS. Baseline medications were continued in both groups. Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS) were used quantitatively for sleep evaluation before and after treatment. The treatment course was 4 weeks.

Results: Sixty PD patients with sleep disorders were enrolled and divided into control (N = 30, age 68.0 ± 5.7-year-old) and treatment (N = 30, 67.6 ± 6.9-year-old) groups. The sleep scores were significantly decreased in both groups after treatment with Pramipexole ($P < 0.01$ and $P < 0.01$ in ESS and PQSI scores respectively) alone or combined with rTMS ($P = 0.004$ and $P < 0.01$). The effect size for ESS score was large (Cohen's d = 0.91 and Cohen's d = 1.01 respectively) and was even larger for PQSI score (Cohen's d = 1.89 and Cohen's d = 2.23 respectively) in the control and treatment groups. Additionally, combination of Pramipexole with rTMS had a better therapeutic effect ($P = 0.028$ and $P = 0.001$). The effect size for ESS score was medium (Cohen's d = 0.58), while the effect size for PQSI score was larger (Table 1).

Conclusions: Combination therapy of Pramipexole with rTMS can further improve sleep quality in PD patients.

Keywords

Parkinson's disease, Pramipexole, rTMS

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease. The clinical manifestations are characterized by resting tremor, bradykinesia, rigidity

Table 1: General information, ESS and PQSI scores and statistical analysis of the control and treatment groups.

Group	Gender (Male, %)	Age (year-old)	Courses (year)	ESS score				PQSI score			
				Before	After	P vale	Cohen's d	Before	After	P value	Cohen's d
Control (n = 30)	20 (66.7)	68.0 ± 5.7	4.6 ± 2.9	7.20 ± 1.51	6.01 ± 1.08	0.004	0.91	8.22 ± 1.84	5.27 ± 1.23	< 0.001	1.89
Treatment (n = 30)	15 (50)	67.6 ± 6.9	3.0 ± 1.9	6.45 ± 1.05	5.48 ± 0.71	< 0.001	1.01	7.82 ± 2.04	3.49 ± 1.41	< 0.001	2.23
P value	0.719	0.823	0.194	0.095	0.028			0.428	0.0011		
Cohen's d					0.58				1.35		

and postural instability. There are also non-motor symptoms (NMS) of PD such as early olfactory loss; sleep disorders such as insomnia; daytime sleepiness with sleep attacks; restless legs syndrome (RLS); and REM sleep behavior disorder (RBD). The main pathological changes are degeneration and loss of dopaminergic neurons in the substantia nigra causing dopamine depletion in the striatum, and the presence of Lewy bodies in the surviving neurons. The NMS in PD are related to widespread distribution of α-synuclein pathology which, in addition to the dopaminergic striatonigral system, involves non-nigral brainstem nuclei, sympathetic, parasympathetic, enteric and pelvic plexuses, cardiac systems, and other organs [1].

Levodopa is the main drugs for the treatment of PD. Its effectiveness may fade over the course of treatment and then cause significant motor fluctuations, such as on-off, wearing off, freezing, involuntary movements in patients [2]. Pramipexole, a non-ergot dopamine receptor agonist, can be used as monotherapy or adjunct agent to treat many PD symptoms such as stiffness, tremors, muscle spasms, and poor muscle control alone or together with levodopa in treating advanced PD patients. Early use of pramipexole may delay or prevent levodopa-induced dyskinesia and motor fluctuations, and may postpone the need for levodopa treatment for several years [3].

PD medications may interfere with sleep circadian causing insomnia at night and hypersomnia during daytime which significantly impact quality of daily living [4]. Sleep disorders including insomnia, daytime sleepiness with sleep attacks, RLS, and RBD affect between 55 and 80 percent of PD patients [5, 6]. Significantly, sleep disorders aggravate patients' cognitive impairment and mental symptoms. Notably, sleep difficulty was ranked as one of the most troublesome nonmotor symptoms in a survey of PD patients of both early- and late-stage [7].

Repetitive transcranial magnetic stimulation (rTMS) is a new neuroelectrophysiological technology that excites or inhibits local cerebral cortical function by changing the stimulation frequency. rTMS can be dosed with high and low frequencies. High frequency (HF) is frequency above 1 Hz, more typically set at ~ 10 Hz. HF has been shown to have an excitatory effect [8]. On the other hand, low frequency (LF) rTMS includes frequencies 1 Hz and below. LF rTMS, when used continuously, is thought to be inhibitory [8]. Pascual-Leone et al. first applied TMS to the treatment of PD patients in 1994 and achieved significantly beneficial results [9]. Positive effect of TMS on sleep in PD patients was also reported [10]. A recently randomized, sham-controlled study demonstrated that LF rTMS over the right dorsolateral prefrontal cortex (DLPFC) improved motor symptoms, depression and cognitive performance in patients with PD [11]. LF rTMS on right DLPFC could be a potential selection in managing motor and nonmotor symptoms in PD [11]. There are a growing number of TMS studies on treating PD symptoms and sleep disorders in those patients. Van Dijk et al. studied sleep using actigraphy and a pressure sensitive pad in 13 patients with PD using 5 Hz rTMS over the motor or the parietal cortex. rTMS over the parietal, but not the motor cortex improved sleep fragmentation and sleep efficiency and decreased the average duration of nocturnal awakenings [10]. Antczak and colleagues studied 11 patients (10 completed) using 15 Hz rTMS bilaterally over the primary motor areas at 120% Motor Threshold (MT), using the PD Sleep Scale and PSG findings, they found decreased NREM stage 1 and nocturnal arousals as well as subjective improvement by patient's report. Jiang and colleagues reported rTMS improved both slow wave sleep and REM sleep [12]. LF rTMS stimulating the right DLPFC or the posterior parietal cortex was found to be effective to reduce cortical hyperexcitability and improve the sleep quality in subjects with chronic primary insomnia [13]. rTMS treatment can improve the sleep architecture and significantly decreases the body awakening level and provides a better long-term treatment effect [11]. The modulatory effect was locally inhibited when 1 Hz rTMS was applied to the occipital cortex [14], However, controversy exists. A study of LF rTMS over the vertex on sleep in PD did not show significant clinical benefit [15].

Although administration of either pramipexole or rTMS improves the sleeping circadian in PD patients, there are currently no reports on combination of pramipexole with rTMS in the treatment for PD sleep disorders. This study aims to observe whether combination of pramipexole with rTMS bears a better therapeutic effect over pramipexole or rTMS alone on sleep disorders in PD patients.

Materials and Methods

Patient selection

Inclusion criteria: 1. Meet the PD diagnostic criteria [16]; 2. Able to complete the test scale evaluation; 3. Age ≤ 80 years

old; 4. Willing to participate in this research study and sign an informed consent form. Exclusion criteria: 1. Parkinsonism (including traumatic, tumor, drug-induced, toxic, vascular and hydrocephalus, etc.) and Parkinson-plus syndromes; 2. Having other diseases that may affect sleep such as chronic obstructive pulmonary disease, coronary heart disease, and stroke; 3. Patients with a history of brain surgery or epilepsy; 4. Pacemakers or intracranial stents and other metal implants; 5. Severe diseases of other systems; 6. Those who cannot cooperate with treatment.

Sixty PD patients with sleep disorders were selected based on the inclusion criteria from the pool of PD patients who were seen at the clinic of the Department of Neurology in the Affiliated Hospital of Weifang Medical College between October 2019 and March 2020. These patients were randomly divided into two groups by a random number table, 30 patients in each group.

Setting

Control group

All patients continued to have the original dose of Levodopa and Benserazide hydrochloride tablets for basic treatment, plus pramipexole hydrochloride tablets (Boehringer Ingelheim Pharmaceutical Co., Ltd.). The initial dose was 0.25 mg/day, and then the dose was increased every 7 days. If the patient could tolerate it, the dose should be increased to achieve the maximum effect. The treatment plan for each patient was personalized, starting with a low dose, gradually titrating up the dose and the treatment course was 4 weeks.

Treatment group

TMS treatment was added to the treatment regimen for the control group. The TMS treatment parameters were the same. The frequency was 1 Hz, and 80% of the motor threshold (MT) stimulation intensity was given. The target was in the right DLPFC and occipital area. Each target point was given 600 pulses in 20 minutes per day. The treatment course was 10 days.

Main outcome measures

The patients were evaluated before and after treatment using the Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS). The scores of the patients' sleep status was recorded.

Statistical analysis

SPSS 21.0 statistical software was used to analyze the data. All the data was expressed as mean ± standard deviation, Paired t-test was used for pairwise comparisons within groups. Independent-sample t-test was used for pairwise comparisons between groups; χ^2 test was used for comparisons between groups. $P < 0.05$ indicated that the difference was significant.

Cohen's d was used to measure the effect size. Effect size is a quantitative measure of the magnitude of the treatment effect. The larger the effect size the stronger the relationship between the control and treatment groups. Small effect = 0.2; Medium Effect = 0.5; Large Effect = 0.8.

Results

There were 20 males and 10 females in the control group with an average age of 68.0 ± 5.7-year-old, 15 males and 15 females in the treatment group with an average age of 67. 6 ± 6.9-year-old. The age range of selected patients was between 51 and 80-year-old. There was no significant difference between the two groups such as gender, age, course of disease, etc., ($p > 0.05$) (Table 1).

The ESS sores were obtained before and after the treatment, it was 7.20 ± 1.51 and 6.01 ± 1.08 for the control group, and 6.45 ± 1.05 and 5.48 ± 0.71 for the treatment group. There was no significant difference between the two groups before ($P = 0.095$), but significant difference after treatment ($P = 0.028$). There were significant differences before and after treatment within each group ($P < 0.05$). The effect size for ESS score before and after treatment was large in the control group (Cohen's $d = 0.91$) and in the treatment group (Cohen's $d = 1.01$) (Table 1).

The PSQI scores were obtained before and after the treatment in both groups. The scores were 8.22 ± 1.84 and 5.27 ± 1.23 for the control group; 7.82 ± 2.04 and 3.49 ± 1.41 for the treatment group. There was no significant difference between these two groups before treatment ($P = 0.428$), but significant difference after treatment ($P = 0.001$) (Table 1). The effect size was large for PQSI score before and after treatment in the control group (Cohen's $d = 1.89$) and in the treatment group (Cohen's $d = 2.23$) (Table 1).

There were significant differences before and after treatment within each group ($P < 0.001$). Additionally, combination of Pramipexole with rTMS had a better therapeutic effect ($P = 0.028$ and $P = 0.001$). The effect size for ESS score was medium (Cohen's $d = 0.58$), while the effect size for PQSI score was larger (Cohen's $d = 1.35$) (Table 1).

Discussion

Motor symptoms are the main clinical manifestations of PD. NMS gradually increase its impact on the quality of life in PD patients as the disease progresses. The presence of a REM sleep behavior disorder in PD patients might reflect the early involvement of dopaminergic neurotransmission in REM sleep-related structures [17] and these structures are affected by imbalanced dopamine levels. Neurons in the substantia nigra pars compacta and in the ventral tegmental area are active during REM sleep and sleep-related disorders may occur when these neurons are targeted such as by neurotoxins [17].

Levodopa continues to be a cornerstone agent in treating PD motor symptoms, however, it may also aggravate the patient's NMS. Side effects of levodopa therapy vary which may cause debilitating iatrogenic conditions including psychiatric symptoms, dyskinesias, or motor fluctuations such as the wearing-off or on-off phenomena. Clinically available new medications such as dopamine receptor agonist have several advantages over levodopa. Nowadays, dopamine receptor agonists can be used as the first choice as monotherapy

for young parkinsonian patients to postpone the initiation of levodopa therapy. For patients with PD at advanced stages, they can also be used as adjunct therapy together with levodopa to retard the development of levodopa-induced motor complications. Pramipexole is a one of the dopamine receptor agonists and is a synthetic derivative of thiazole. Pramipexole stimulates dopamine receptors in the striatum and restore the dopamine signals required for the normal function of the basal ganglia in PD patients, thereby achieving the effect of treating PD [18, 19]. Pramipexole binds to the dopamine D_3/D_2 receptors in the emotional regulation area outside the striatum and improves dopamine effects on cerebral cortex-frontal lobe and limbic system [20]. Experimental *in vitro* and *in vivo* studies suggest neuroprotective activities of pramipexole via its dopamine auto receptor agonist property as well as interaction with the D_3 receptor, including antioxidant effect, blocking mitochondrial permeability of transition pore, stimulating release of trophic factors, inhibiting apoptotic pathways, promoting expression of neurotrophic factors [20].

In our control group, the ESS and PSQI scores were significantly reduced after 4-week of treatment with pramipexole only ($P < 0.01$). The effect size was large for ESS score (Cohen's $d = 0.91$) and large for PSQI scores (Cohen's $d = 1.89$) (Table 1). Our study also showed that Pramipexole can improve the symptoms of sleep disorders in PD patients.

rTMS is a simple and safe neuro-electrophysiological technology that can effectively stimulate the cerebral cortex by magnetic signals that can pass through the skull without attenuation. When rTMS acts on the cortex in a specific area, it can induce the release of dopamine under the cortex, improve cortical excitability and normalize abnormally activated local neuronal networks, thereby improving clinical symptoms [21]. rTMS has been reported to be effective for PD and this technique is gradually being widely used clinically [22]. Factors affecting rTMS include stimulation of the anatomic target, intensity and frequency [14]. Among these factors, low range of frequency seems to be the most important parameter of rTMS [23]. Additionally, rTMS has broad effects on various neurotransmitters and their transmission in the brain, a variety of receptors including those for serotonin and N-formyl D-aspartate in different brain locations. It can also modulate the expression of genes that regulate neuronal excitability underlying mechanisms that regulate the state of brain function [21, 24, 25]. On the other hand, NMS may be related to a variety of neurotransmitter metabolism disorders such as 5-hydroxytryptamine (5HT), norepinephrine (NE), dopamine (DA) [26]. It has been hypothesized that 5-HT plays a role in sleep-wake cycle controlling and also promotes the release of γ-aminobutyric acid, which slows down neuronal activity, and inhibits the related functions of the reticular ascending activation system distributed on the brainstem, non-rapid eye movement sleep increases, thereby improving the patient's sleep quality [27-30]. Apparently, treating NMS can also improve the patients' quality of life.

In this study, the ESS score of the treatment group was significantly lower than those before treatment ($P < 0.001$), the effect size was large (Cohen's $d = 1.01$); the PSQI score of the treatment group also was significantly lower than those before treatment ($P < 0.001$), the effect size was large (Cohen's $d = 2.23$). The ESS and PSQI scores were significantly lower than those of the control groups ($P = 0.028$ and $P = 0.0011$ respectively), with medium and large effect size for ESS and PSQI scores respectively (Cohen's $d = 0.58$ and Cohen's $d = 1.35$) (Table 1), indicating that pramipexole combined with rTMS has a significant effect on sleep disorders in PD patients.

In conclusion, Pramipexole can improve the symptoms of sleep disorders in PD patients. Pramipexole combined with rTMS can provide a better therapeutic effect on sleep disorders in PD patients and further improve their quality of life.

Further randomized, sham-controlled studies with large number of patients are needed in the future as the current study did not include sham control with small sample numbers. Quantitate sleep scoring, cognitive scoring, depression scoring, and different sleep types of analysis could also be included in further studies.

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