Neurol Sci (2017) 38:249–254
DOI 10.1007/s10072-016-2748-x

ORIGINAL ARTICLE

Repeated sessions of transcranial direct current stimulation evaluation on fatigue and daytime sleepiness in Parkinson's disease

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Received: 18 April 2016 / Accepted: 21 October 2016 / Published online: 31 October 2016

Abstract Parkinson is a common and disabling disease that affects patient's and career's quality of life. Unfortunately, medications, such as dopaminergic and sedative-hypnotic drugs, as an effective treatment have unwilling side effects. Recently, Transcranial Direct Current Stimulation (tDCS) in conjunction with medication becomes popular as a complementary safe treatment and several studies have proved its effectiveness on controlling motor and specially non-motor aspects of Parkinson's disease. In this randomized double-blind parallel study, 23 patients with Parkinson's disease divided into two groups of real tDCS plus occupational therapy and sham tDCS plus occupational therapy and the effects of therapeutic sessions (eight sessions tDCS with 0.06 mA/cm^2 current, 20 min on dorsolateral prefrontal cortex) were evaluated on fatigue and daytime sleepiness just after therapeutic course and in 3-month follow-up. tDCS had a significant effect on fatigue and no effect on daytime sleepiness reduction in patients with Parkinson's disease. tDCS is an effective and safe complementary treatment on fatigue reduction in Parkinson's disease.

Keywords Transcranial direct current stimulation · Parkinson's disease · Fatigue · Daytime sleepiness

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Introduction

Parkinson's disease (PD) is an extra pyramidal chronic neurodegenerative disease of brain mainly characterized by a progressive degeneration and necrosis of dopaminergic neurons in substantia nigra. The disease affects people mostly in the middle and old-aged [1]. Non-motor symptoms (NMS) are symptoms that do not involve movement, coordination, physical tasks, or mobility. NMS include autonomic dysfunction, cognitive/neurobehavioral disorders, and sensory as well as sleep abnormalities [2].They significantly impair quality of life and cause severe disability but often poorly recognized [3]. Patients suffering from PD are usually appropriately treated for their motor symptoms, while a significant proportion of NMS still goes unreported and is, consequently, not adequately treated [4]. They occur in over 90% of patients with PD across all stages. Fatigue is a common problem, occurring in about 50% of patients and it is often the most troubling of all symptoms of PD. Fatigue is associated with reduced activity and poorer quality of life. It can be either mental, physical, or both. In most studies, the presence and severity of fatigue do not correlate with disease duration or degree of motor disability [5]. Sleep disturbances

and daytime sleepiness are well-known phenomena in PD and were reported in the original description by James Parkinson. Sleep disorders have a complex etiology related not only to the underlying neurodegenerative process, but also to the motor and non-motor features of PD and to dopaminergic therapy. A community-based study revealed that nearly two-thirds of patients reported sleep disturbances, which are significantly more frequently than patients with diabetes and healthy control subjects [6]. Insomnia, hypersomnia, and parasomnia may all occur in PD and contribute to excessive daytime sleepiness. Daytime sleepiness has been reported in almost 50% of patients with PD who were also found to be sleepier than normal controls [7].

tDCS uses a weak direct electrical current which is usually delivered via two surface electrodes [8]. It induces a polarity-dependent excitability shift of the stimulated areas, which is initially induced by a sub-threshold membrane potential shift, followed by prolonged after-effects that depend on modification of the strength of NMDA receptors. tDCS with 2 mA current over the prefrontal cortex seems to be effective in changing connectivity in distinct functional brain networks [9, 10]. Until now, no study has been published on the subject of tDCS effects on reducing fatigue and daytime sleepiness in PD, but, Doruka et al., reported positive effect of tDCS on executive function and also, Boggio et al., reported the same results on working memory in patients with PD [11, 12]. NMS treatment is a challenging issue and few studies have been performed until now, so we decided to evaluate tDCS effects on fatigue and daytime sleepiness reduction in PD. In fact, our purpose was to identify additive effects of consecutive sessions of tDCS in patients with PD.

Materials and methods

Study setting

The study was conducted at Physical Medicine and Rehabilitation department of Firoozgar Hospital in Tehran. This double-blind sham-controlled 3-month trial evaluated the effect of multisession anodal tDCS on left DLPFC to improve fatigue and daytime sleepiness in patients with PD. Each patient received eight sessions of stimulation in 2 week duration and also occupational therapy just after each session. The primary outcome measure of this study was fatigue assuming the effect size of fatigue being 0.8 with alpha set at 0.05, a power of 0.8, and accounting for 15% dropouts, and the sample size needed was calculated as being 15 patients in each group.

Participants

Twenty-three patients (9 women and 14 men) aged between 36 and 80 years (mean age 63 years) with idiopathic PD ended up the study. Inclusion criteria were: all of the patients should be in stage 2 or 3 of Parkinson's disease based on Hoehn and Yahr criteria and also should: be under stable pharmacological regime at least 30 days before entrance in study; be in stable clinical condition to complete the study; have appropriate primary response to Levo-DOPA or its agonists; have normal MRI; not have Parkinson-related dementia using Mini-Cog test; and not have drug-related parkinsonism. Exclusion criteria were patient unwillingness to complete the study and patient inability to complete the study because of any reason at any time during the study. The local ethics committee at the Iran University of Medical Sciences approved the study protocol and it was performed in accordance with the ethical standards of the Helsinki Declaration. Written informed consent was signed by all patients before participation in the study. The trial is registered at the Iranian Registry of Clinical Trials (IRCT) with the reference ID IRCT2015070123012N1.

Intervention

Parkinson's disease is classically categorized in Basal ganglia disorders, but previous studies showed regional cerebral blood flow (rCBF) decrement in the supplementary motor area (SMA), and insular and dorsolateral prefrontal cortex (DLPFC) and there was a correlation between the degree of the rCBF decrement in the DLPFC or the insular cortex and the score of the unified Parkinson's disease rating scale [13]. Differences in neural activity between PD patients OFF medication and healthy controls converged in a left lateralized fronto-parietal cortical network comprising presupplementary motor area, primary motor cortex, inferior parietal cortex, and superior parietal lobule [14]. Bogio et al. study showed a significant effect of active anodal tDCS on LDLPFC with 2 mA current on working memory in 18 patients with PD [12].

According to these results, left DLPF cortex was chosen in our study for anodal tDCS stimulation.

Patients were allocated into real or sham treatment groups using a simple randomization method.

12 patients were assigned to active and 11 patients to sham treatment groups. For all patients (irrespective of more involved side of body), the anode electrode was placed over left DLPFC area that is localized as 5 cm in front of C1 using international 10–20 electroencephalogram system. The cathode electrode was placed over right DLPFC area.

A battery driven stimulator (Activadose II) with a maximum current output of 4 mA generated direct electrical current. We used pairs of 35 cm^2 rubber electrodes covered with 0.9% saline soaked sponges for transmission.

In both conditions (real and sham), the direct current was ramped up to 0.06 mA/cm^2 within 30 s. Experiment group (anodal tDCS group) received 20 min of stimulation with a current intensity of 0.06 mA/cm^2. After the initial ramp-up, in sham group, the current was directly ramped down to 0 and patients felt tingling sensation at the beginning. They received no more stimulation in the remaining time. The ramp-down time was 4 s in both groups. The stimulator was placed out of sight of the patients.

Outcome

Fatigue Severity Index (FSI) (nine items, each 1–7, total score is mean of nine items range 1–7, higher score_increasing severity) was used as outcome measure to evaluate change in patients fatigue level.

Epworth Sleepiness scale (ESS, eight items, each 0–3, total 0–24, higher score_increasing severity) was used as outcome measure to evaluate changes in patients' daytime sleepiness.

Using these two questionnaires, fatigue and daytime sleepiness were evaluated before, just after eight session courses and 3 months later. Participants and rater were both blinded to the treatment.

Statistical analysis

Analysis was performed using the SPSS22 software. Independent sample *t* test and Chi-square test were used for analysis of baseline characteristic. A Greenhouse-Geisser correction was used for sphericity violation. "Kolmogorov–Smirnov" test revealed normal distribution of data, so parametric tests were used. Descriptive statistics were extracted, and "Mixed design ANOVA" was used to explore the main and interaction effects of time and group on FSI and ESS. Statistical significance was set at ≤ 0.05.

Results

40 patients were evaluated, and 30 patients were enrolled in the study based on inclusion criteria. Seven patients did not start treatment, because they decided to use other facilities near their homes.

Twenty-three patients (14 males and 9 females) were randomly allocated to the experiment and sham groups with a mean age of 63 ranging 36–80 years and all of them completed the study. Baseline characteristic of experiment and sham groups is shown in Table 1.

Table 1 Baseline characteristic of experiment and sham groups

Parameter	Mean	Sig
Age (year)		
Experiment	61.33	0.478
Sham	64.81	
Sex (%)		
Experiment	7 female, 5 male	1.000
Sham	7 female, 4 male	
FSI		
Experiment	39.91	0.542
Sham	35.18	
ESS		
Experiment	10.75	0.312
Sham	8.45	

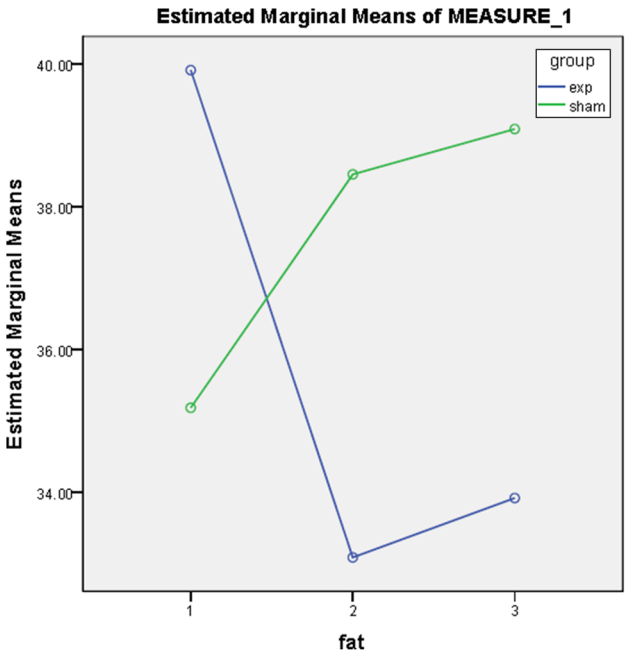

Fig. 1 Groups' interaction and behavior differences between two groups in Fatigue Severity Index. Experiment group showed decrement in FSI, and sham group showed incremental process

For Fatigue Severity Index Score (FSI), there was a significant time-group interaction, showing that the behavior of groups differed regarding changes in FSI ($df = 1.91$, $F = 6.83$, $p = 0.003$), Fig. 1.

The difference was significant between before and just after therapeutic course termination in experiment group ($p = 0.036$). The difference in FSI score was not significant in the sham group at any time point. Pairwise comparisons of FSI in experiment and sham groups are shown in Table 2.

Table 2 Pairwise comparisons of FSI in experiment and sham groups

Group	Different time points	Mean difference	Sig.	95% confidence interval for difference lower bound	95% confidence interval for difference upper bound
Experiment	Just before v/s just after treatment	6.833	0.036	0.406	13.261
	Just before v/s 3-month follow-up	6.000	0.131	−1.421	13.421
	Just after v/s 3-month follow-up	−0.833	1.000	−8.397	6.731
Sham	Just before v/s just after treatment	−3.273	0.436	−9.219	2.674
	Just before v/s 3-month follow-up	−3.909	0.285	−9.997	2.179
	Just after v/s 3-month follow-up	−0.636	0.457	−1.815	0.542

The mean difference is significant at the 0.05 level

Time-group interaction on Epworth Sleepiness scale (ESS) was not significant ($df = 1.53$, $F = 0.60$, $p = 0.50$). In contrast assessment, there was no significant effect in none of two groups at any time point. Although figures revealed decreasing ESS mean between before and just after treatment course in experiment and increasing of mean in sham groups, but the differences were not significant, Fig. 2.

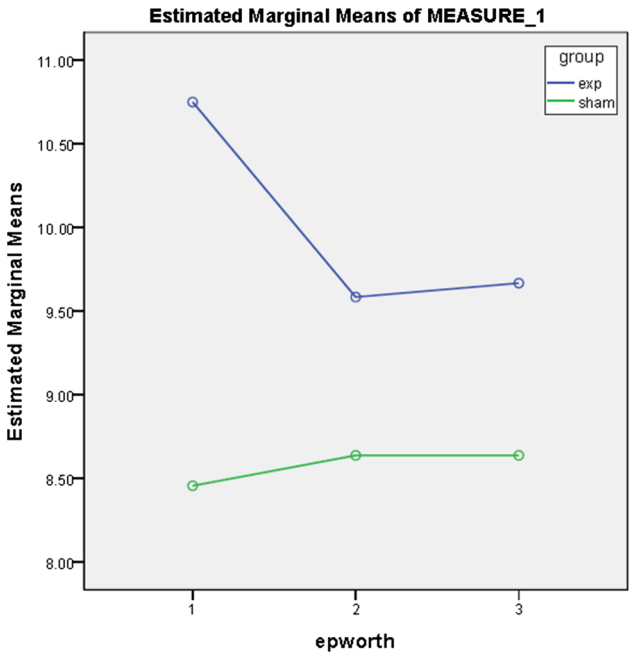

Fig. 2 Groups' interaction in Epworth Sleepiness scale. Experiment group showed decrement, and sham group showed increment process in-between before and just after therapeutic course, but the difference was not statistically significant

Discussion

This randomized double-blind parallel study evaluated left dorsolateral prefrontal cortex anodal tDCS effects on fatigue and daytime sleepiness in Parkinson's disease (PD). We found a significant benefit on fatigue reduction but no significant effect on daytime sleepiness improvement in any time point.

Sleep disorders and fatigue are common complaints of patients with PD and about one-third of patients have depression. Feeling of fatigue and lack of energy and motivation can be categorized in depressive disorder criteria. Needless to say that depression is not the only cause of fatigue presentation in PD and rigidity, dyskinesia, gait impairment, taking compensatory mechanism, and as a result, more energy consumption for activity of daily living performance and also secondary complication of PD are principal causes of fatigue incidence.

Several articles published based on evaluation of tDCS effects in PD and revealed positive effects (on executive function, working memory, and motor improvement), but they are few and not performed in all aspects of PD.

In one study, active stimulation of both left and right DLPFC resulted in prolonged improvement of executive function, compared to sham tDCS at 1-month follow-up in ten participants [11]. Another study showed a significant effect of active anodal tDCS on LDLPFC with 2 mA current on working memory in 18 patients with PD [12].

More studies were performed based on motor effects of tDCS in PD and they showed a significant improvement as well.

In one study, noticeable motor improvement was observed after right DLPFC stimulation vs. placebo stimulation in ten patients with PD [13]. Other authors reported considerable improvement of gait with reduction in number and duration of freezing of gait episodes, along with a significant reduction in the Unified Parkinson's Disease Rating Scale score after anodal stimulation of primary motor cortex in ten participants [15]. Another study showed a positive effect of left DLPFC anodal tDCS on motor function of ten patients [16].

No study has been performed on fatigue and daytime sleepiness in patients with PD until now, but several trials

have been done in other diseases. In study by Ferrucci et al., anodal tDCS applied over the motor cortex resulted in fatigue improvement in 65% of patients with multiple sclerosis [17]. In addition, Saiote et al. reported that anodal tDCS effect on left prefrontal area was correlated with lesion load in left frontal cortex of patients with multiple sclerosis as the patients with higher lesion load responded positively to anodal tDCS [18]. Another study by Acler et al. showed anodal tDCS over both promoter areas improved sleep and fatigue symptoms in patients with post-polio syndrome [19].

Considering these results, we decided to conduct a study on fatigue and daytime sleepiness in patients with PD. Our study was the first RCT in this field.

The results of our study were in line with previous studies and revealed a positive effect of anodal tDCS on fatigue reduction in short time and also 3-month follow-up in patients with PD.

Several studies have been conducted to examine the efficacy of tDCS in treating depression in healthy people and most of them demonstrated that active tDCS was effective in reducing depressive symptoms [20–24].

It is likely that the probable cause of tDCS effectiveness on fatigue in PD is its positive effects on mood and depressive symptoms, but further synchronous studies with more sample size on mood and physical energy in patients with PD should be considered.

There is no difference in daytime sleepiness reduction between experiment and sham groups at any time point.

We should mention that one limitation of our study was low baseline score in ESS of patients at the beginning of the study (baseline score mean in experiment group was 10.75 and in sham group was 8.45). This point can explain the result, so further studies with more sample size on patients with more severe daytime sleepiness are needed. Other aspects of sleep disorders in PD, such as quality of overnight sleep, should be targeted in future studies as well as modifications in research protocols, including different stimulation sites, tDCS polarity, duration, and intervals of treatment.

Another limitation was short duration of follow-up. Furthermore, considering more objective outcome measures, such as functional imaging, will be of benefit in detection of subclinical changes in cortical excitability.

Conclusions

Based on the results of the present study, tDCS is an effective treatment on fatigue reduction in Parkinson's disease. However, there is no significant effect on daytime sleepiness in any time point.

Acknowledgements We are grateful to patients who participated in this project and Pouria Ghaboussi, MD for his help in identification of treatment protocol.

Compliance with ethical standards

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

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