Assessment of the Effect of Subthalamic Deep Brain Stimulation on Sleep Quality of Parkinson’s Disease Patients

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ABSTRACT

AIM: To investigate the effects of subthalamic deep brain stimulation (STN DBS) therapy on sleep quality of Parkinson’s Disease (PD) patients and the relationship between sleep, motor symptoms, depression, and adverse effects of dopamine replacement therapies.

MATERIAL and METHODS: A total of 26 PD patients have been included and assessed using various tools both 1 week before and 8 months after the STN DBS therapy. The data collection tools were the Unified Parkinson’s Disease Rating Scale (UPDRS), Beck Depression Inventory (BDI), Montreal Cognitive Assessment (MoCA), Parkinson’s Disease Questionnaire (PDQ-39), Pittsburgh Sleep Quality Index (PSQI), Insomnia Severity Index (ISI), Epworth Sleepiness Scale (ESS) and Polysomnography.

RESULTS: PSQI, ISI, and ESS scores were found to have significantly improved after the STN DBS therapy (p=0.002, p=0.006, p<0.001, respectively), as were the scores obtained from several PSQI sub-scales, that is, sleep duration, sleep disturbance and daytime dysfunction (p=0.023, p=0.005, p=0.032, respectively). Additionally, Wake Times After Sleep Onset (WASO) (p=0.047) and Rapid Eye Movement (REM) sleep latency values (p=0.005) were found to have decreased after the STN DBS treatment, whereas REM sleep durations (p=0.028) and REM sleep percentages (p=0.007) were found to have increased, after the STN DBS therapy. No correlation was found between the ESS scores and Levodopa Equivalent Dosage (LED) or between the scores obtained from the sleep scales and the scores obtained from the UPDRS and BDI. There was also no correlation between sleep scores and other PD-related factors.

CONCLUSION: The findings of this study indicated that STN DBS therapy positively affected the PD patients’ sleep. This result was attributed to the neuromodulatory effects of the STN DBS independent of the motor symptoms, depression levels, and LED decrease.

KEYWORDS: STN-DBS, Parkinson’s disease, Sleep

INTRODUCTION

Parkinson’s Disease (PD) is a progressive neurodegenerative disorder that manifests with both motor and nonmotor abnormalities. Sleep problems are important non-motor complications of PD, which adversely affect patients’ quality of life (19,27).

Bilateral deep brain stimulation of the subthalamic nucleus (STN DBS) is a widely accepted treatment option for relieving the motor symptoms of, and reducing the need for dopaminergic medication in, advanced-stage PD patients with frequent motor fluctuations (11,13,27). Improvements observed in different night time sleep parameters following the STN DBS therapy have been addressed in many studies (2,4,10,16,21,22,24). The effect of STN DBS on excessive daytime sleepiness (EDS) remains to be controversial, as well (8,17,27). It was reported in some studies that bilateral DBS had no effect on excessive daytime sleepiness (EDS), contrary to other studies, in which it was reported that bilateral DBS positively affected EDS (6,9,20). Sleep alterations observed following the STN DBS therapy may be attributed to the DBS’s therapeutic modulation or other possible concomitant factors such as relieving of post-operative motor symptoms, reductions in LED or cognitive and psychiatric changes.

The research data in respect of STN DBS therapy, including detailed data obtained from sleep assessment scales and polysomnography (PSG) along with concomitant psychiatric, cognitive and motor scales, need to be analyzed comprehensively in order to determine whether the sleep alterations observed following the STN DBS therapy are due to mood alterations, withdrawal of levodopa, improvements in motor complications or the intrinsic neuromodulatory effects of STN DBS (27). Additionally, contrary to the majority of the studies available in the literature, which were conducted with a limited number of patients, large-scale studies are needed in order to obtain more conclusive results.

In view of the foregoing, this study was designed as a comprehensive study in order to investigate the effects of STN DBS therapy on sleep quality of PD patients, and to fill the said gap in the literature in this regard.

MATERIAL and METHODS

This study was carried out as a prospective observational study. The study protocol was approved by the Ethics Committee of Marmara University (Date: 04.12.2015; protokol no: 09.2015.348), Istanbul, and the research was conducted in accordance with the Declaration of Helsinki. Informed consents were obtained from all patients included in the study.

Patient Selection

A total of 26 advanced-stage PD patients, who were deemed eligible for STN DBS via the core assessment program for surgical interventional therapies in Parkinson’s Disease (CAPSIT-PD) and followed up in the Movement Disorders and PD Outpatient Clinic of Marmara University Hospital between June 2015 and May 2017, were included in the study. The relevant surgical procedures were carried out by the DBS therapy group, which includes a movement disorders specialist, an experienced neurosurgeon, and a neuropsychologist.

Data Collection

The research data were collected via face-to-face interviews with patients or obtained from caregivers and patient files. Unified Parkinson’s Disease Rating Scale (UPDRS), Parkinson’s Disease Questionnaire (PDQ-39), Montreal Cognitive Assessment (MoCA), Beck’s Depression Inventory (BDI), Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Insomnia Severity Index (ISI) and polysomnography (PSG) were used to assess various sleep characteristics of the PD patients. In addition, sociodemographic data of the patients were collected and the Levodopa Equivalent Dosages (LEDs) were calculated for each patient.

Surgical Procedure

Intraoperative microelectrode recording (MER) procedure was used for precision targeting in all procedures of DBS placement. MER was initiated at 10 mm above the target and continued till the onset of substantia nigra pars reticulata (SNr) activity. The longest microelectrode recordings in STN were used for the stimulation. Patients were examined by the neurologist (D.I.G.) during the surgical procedure. The stimulus intensity was increased to the point where the best clinical improvement was obtained without any side effects. The permanent electrode position was verified using fluoroscopy. The same procedure was performed for the contralateral side. T1-weighted (longitudinal relaxation time) and T2-weighted (transverse relaxation time) magnetic resonance imaging (MRI) scans were obtained postoperatively within 24 hours of the surgical procedure to verify the electrode location.

Clinical Assessment

All evaluations were performed twice, both during the week before the implantation of the DBS electrode and an average of 8 months after the implantation of the DBS electrode. Motor outcomes were assessed using the UPDRS performed under medication. Patients were administered controlled-release levodopa/benserazide 1–2 hours before bedtime to avoid symptoms of drug withdrawal. PDQ-39 was used to assess patients’ quality of life, MoCA was used for cognitive assessment, and BDI was used for psychiatric evaluation. LEDs were calculated for each patient, as well as for each medication used, that is, dopamine agonists, MAO-B and COMT inhibitors.

ESS was used to assess excessive daytime sleepiness. ESS scores of > 10 were deemed to have indicated subjective

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excessive daytime sleepiness. ISI, a self-report questionnaire, was used to assess the nature, severity, and impact of insomnia. ISI scores of >22 were deemed to have indicated severe insomnia. PSQI, which consists of seven subscales, i.e. subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medication, and daytime dysfunction, was used to assess several aspects of sleep. Total PSQI scores ranged from 0 to 21 and lower PSQI scores were deemed to have indicated better sleep quality.

Polysomnography

Polysomnography (PSG) was carried out using an Embla N7000 recording system and in accordance with the standard criteria set out by the American Academy of Sleep Medicine (AASM). Experienced sleep specialists (G.S. and K.A.) scored all recordings. The following parameters were assessed: total sleep time, stage of sleep, sleep efficiency, WASO, REM latency, length of time and percentage of time spent in each sleep stage (NREM1, NREM2, NREM3 and REM), apnea-hypopnea index, oxygen saturation and periodic leg movements.

Statistical Analysis

R-2.15.3 (R Core Team, 2013) software package was used to conduct the statistical analyses. Shapiro-Wilk test and graphical examination were used to analyze the distribution of the quantitative data. Dependent samples t-test was used to analyze normally distributed variables, and Mann-Whitney U test (Wilcoxon signed-rank test) was used to analyze non-normally distributed variables. Bivariate correlation analysis was carried out via Pearson's and Spearman's correlation analyses for normally distributed variables and non-normally distributed variables, respectively. Probability (p) values of <0.05 were deemed to have indicated statistical significance.

RESULTS

A total of 26 PD patients, who were found eligible for STN DBS, were included in the study. Of the 26 patients, a total of 7 patients could not be assessed via post-operative PSG due to various reasons. Three of these patients could not be assessed due to social reasons, another 3 could not be assessed due to device failure, and 1 patient could not be assessed due to a critical wound infection. PSG recordings of 9 patients could not be scored for technical reasons. All patients completed the pre-treatment and post-treatment assessments, whereas 10 patients completed both the pre-treatment and post-treatment assessments, and the pre-operative and post-operative PSG.

Demographics

Mean disease duration was calculated as 13.73 ± 5.35 years (min. 5 and max. 25 years), whereas the age of disease onset was found to have varied between 19 and 62 years, with an average of 43.35 years.

Comparison of Post-Treatment Subjective Sleep Scale Scores

After the treatment, PDA-39 scores were found to have improved (p=0.013), whereas LED values were found to have decreased by around 20% (p=0.001). Additionally, UPDRS total scores (p<0.001), ESS score (p=0.006), ISI score (p=0.001), mean total PSQI score (p=0.002) along with the scores obtained from the PSQI subscales of subjective sleep quality (p=0.007), sleep duration (p=0.023), sleep disorder (p=0.005) and daytime dysfunction (p=0.032), were all found to have significantly decreased after the treatment (Table I: Comparison of Post-Treatment Subjective Sleep Scale Scores).

Comparison of Sleep Scale Scores with BDI and UPDRS Total Scores

The correlations between sleep scale scores and changes in BDI and UPDRS scores are shown in Table II entitled “Relationship between PSQI, ESS, ISI scores and BDI and UPDRS total scores”.

Comparison of LED and ESS Scores

No significant relationship was found between the LED and ESS scores (r=0.088, p>0.05) (Table III: Relationship between LED and ESS).

Pre-Treatment and Post-Treatment PSG Data

After the treatment, WASO (p=0.047) and REM latency (p=0.005) values were found to have decreased, whereas the duration of REM (p=0.028) and the percentage time spent in REM were found to have increased (p=0.007) (Table IV: Pre-Treatment and Post-Treatment PSG Data).

DISCUSSION

In this study, the effect of STN DBS on sleep quality was investigated through the assessment of the possible effects that might have stemmed from any probable confounding factors, including motor and other non-motor changes. In this context, in parallel with the respective results reported in the literature (14, 15), significant improvements were observed in the post-treatment scores obtained from the subjective nocturnal sleep scales, that is, ISI, total PSQI, PSQI subscales of sleep duration, sleep disturbance and daytime dysfunction. The few published studies, in which PSG was used to assess the sleep changes that occurred following the STN DBS therapy, mostly reported improvements in sleep architecture (2,4,10,16,22,24). Sleep efficiency, i.e. total sleep time in the overall bedtime period, was found to have improved between 40% to 80% following the STN DBS therapy in some studies.
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In another study, scores obtained from the sleep scales were found to have improved after the STN DBS therapy, yet the PSG parameters, i.e. total sleep time, sleep efficiency, N3 and REM sleep time, all of which had decreased, were found to have deteriorated, and the WASO values were found to have increased (14). In comparison, in this study, PSG results revealed an improvement in sleep efficiency in 8 out of the 10 patients, albeit not statistically significantly. In addition, in line with the respective results reported in the literature (2,4,10,16,27,28), REM sleep latency values were found to have decreased after the STN DBS therapy.

Table I: Difference in Subjective Sleep Scales After Treatment

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
<th>Test Value</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI</td>
<td>Avg ± sd 11.58 ± 7.59</td>
<td>Avg ± sd 11.19 ± 7.83</td>
<td>0.334</td>
<td>0.741</td>
</tr>
<tr>
<td>UPDRS Total</td>
<td>45.5</td>
<td>29</td>
<td>-3.957</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>PDA-39</td>
<td>50.11 ± 26.99</td>
<td>30.04 ± 25.10</td>
<td>-2.685</td>
<td>0.013*</td>
</tr>
<tr>
<td>LED</td>
<td>913.46 ± 264.41</td>
<td>709.77 ± 269.28</td>
<td>-3.920</td>
<td>0.001*</td>
</tr>
<tr>
<td>PSQI</td>
<td>10 ± 6.14</td>
<td>7 ± 3.11</td>
<td>-3.107</td>
<td>&lt;0.002**</td>
</tr>
<tr>
<td>PSQI- Sleep latency</td>
<td>2 ± 1.2</td>
<td>1 ± 0.2</td>
<td>2.676</td>
<td>&lt;0.007**</td>
</tr>
<tr>
<td>PSQI- Sleep duration</td>
<td>3 ± 1.3</td>
<td>1.5 ± 1.3</td>
<td>2.266</td>
<td>&lt;0.023*</td>
</tr>
<tr>
<td>PSQI- Sleep efficiency</td>
<td>1 ± 0.3</td>
<td>0.5 ± 0.3</td>
<td>1.784</td>
<td>&lt;0.074</td>
</tr>
<tr>
<td>PSQI- Sleep disturbance</td>
<td>1.5 ± 1.2</td>
<td>1 ± 1.1</td>
<td>2.828</td>
<td>&lt;0.005**</td>
</tr>
<tr>
<td>PSQI- Use of sleep medication</td>
<td>0 ± 0.0</td>
<td>0 ± 0.2</td>
<td>-1.029</td>
<td>&lt;0.303</td>
</tr>
<tr>
<td>PSQI- Daytime dysfunction</td>
<td>1 ± 0.2</td>
<td>1 ± 0.1</td>
<td>2.149</td>
<td>&lt;0.032*</td>
</tr>
<tr>
<td>ESS</td>
<td>11.38 ± 6.60</td>
<td>8.58 ± 5.9</td>
<td>2.988</td>
<td>&lt;0.006**</td>
</tr>
<tr>
<td>ISI</td>
<td>12.5 ± 5.20</td>
<td>5 ± 3.13</td>
<td>-3.362</td>
<td>&lt;0.001**</td>
</tr>
</tbody>
</table>

*Dependent groups t-test  Wilcoxon signed-ranks test  *p<0.05  **p<0.01


Table II: Relationship Between PSQI, ESS, ISI and BDI, and UPDRS Total Scores

<table>
<thead>
<tr>
<th></th>
<th>PSQI Change</th>
<th>ESS Change</th>
<th>ISI Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
<td>r</td>
</tr>
<tr>
<td>BDI Change</td>
<td>0.333</td>
<td>0.097</td>
<td>0.111</td>
</tr>
<tr>
<td>UPDRS Change</td>
<td>-0.044</td>
<td>0.831</td>
<td>-0.157</td>
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</tbody>
</table>

*Spearman’s correlation coefficient  *Pearson’s correlation coefficient  *p<0.05


Table III: Relationship between LED and ESS

<table>
<thead>
<tr>
<th></th>
<th>LED Change</th>
<th>ESS Change</th>
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<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td>BDI Change</td>
<td>0.088</td>
<td>0.670</td>
</tr>
</tbody>
</table>

*Pearson’s correlation coefficient  p>0.05

ESS: Epworth sleepiness scale, LED: Levodopa equivalent dosage.
In conclusion, the results of both the subjective and objective assessments carried out within the scope of this study suggest that STN-DBS therapy has a positive effect on nocturnal sleep quality and architecture. However, the therapeutic mechanism underlying the effects of STN-DBS on sleep physiology is yet to be clarified (3,8,17,27). Two possible mechanisms have been hypothesized in the literature. In the first one, post-operative sleep quality improvement has been attributed to the neuromodulatory effect of STN DBS therapy, taking into consideration STN's role in the sleep-wake regulation due to its close location to the wake-promoting midbrain areas (8,18,23,26). In the second one, post-operative sleep quality improvement has been attributed to the relief of nocturnal mobility/motor symptoms or alterations in nonmotor symptoms such as depression and cognition (8,27).

The relationship between motor symptoms and night-time sleep has been addressed in two studies only (4,14). In one of these studies, a correlation was found between the sleep efficiency and UPDRS-III scores (4), whereas in the other, no association was found between the motor symptoms (UPDRS score) and the Parkinson’s disease sleep scale (PDSS) score (14). In comparison, in this study, no correlation was found between the UPDRS scores and the ISI, PSQI or ESS scores.

Despite the commonly uttered effect of depression on sleep, the relationship between depression and sleep is often

<table>
<thead>
<tr>
<th>Table IV: Evaluation of Pre- and Post-Treatment Changes of PSG Data</th>
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<tbody>
<tr>
<td><strong>Before</strong></td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Total Recording Time (Min)</td>
</tr>
<tr>
<td>Total Sleep Time (Min)</td>
</tr>
<tr>
<td>Total Awake Time (Min)</td>
</tr>
<tr>
<td>Sleep Efficiency</td>
</tr>
<tr>
<td>Total Number of Wakes</td>
</tr>
<tr>
<td>NREM1 Time (Min)</td>
</tr>
<tr>
<td>NREM1 Percentage</td>
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<tr>
<td>NREM2 Time (Min)</td>
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<tr>
<td>NREM2 Percentage</td>
</tr>
<tr>
<td>NREM3 Time (Min)</td>
</tr>
<tr>
<td>NREM3 Percentage</td>
</tr>
<tr>
<td>REM Time (Min)</td>
</tr>
<tr>
<td>REM Percentage</td>
</tr>
<tr>
<td>REM Latency</td>
</tr>
<tr>
<td>Apnea Hypopnea Index</td>
</tr>
<tr>
<td>PLMI</td>
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</table>

*Wilcoxon signed-rank test  **p<0.01  **p<0.05


It was reported in many studies that STN DBS therapy did not have any positive effect on the number of awakenings or sleep latency (10,16,22). Yet, in one of these studies, an improvement was reported in the post-operative arousal index following the administration of STN DBS therapy (16). In comparison, in this study, a decreasing trend was observed in the number of awakenings after the STN DBS therapy, yet it was not statistically significant.

A significant decrease in post-treatment WASO values was reported in one study (21), a decreasing trend in post-treatment WASO values was reported in other studies albeit not statistically significant (16,22), whereas no difference in post-treatment WASO values was reported in the majority of the studies (2,10,24). In comparison, in this study, a significant decrease was observed in WASO values after the administration of STN DBS therapy.

An increase in slow-wave sleep and REM sleep times was reported in some studies following the administration of STN DBS therapy (22,24). On the other hand, in another study, it was reported that the REM sleep disturbances were refractory to STN DBS, whereas that the sleep duration, sleep efficacy, slow-wave sleep and daytime sleepiness were improved. In comparison, in this study, an increase was observed in the REM sleep durations and in the percentages of time spent in REM sleep after the STN DBS therapy.

Despite the commonly uttered effect of depression on sleep, the relationship between depression and sleep is often
disregarded when conducting studies. Thus, the relationship between sleep improvement and the neuromodulatory effect or mood alterations remains uncertain (15). In the only study that addressed the said relationship, a significant correlation was found between depression and sleep (14). In comparison, in this study, no correlation was found between the sleep scale scores and the BDI scores and improved UPDRS scores. Based on the findings of this study and the results reported in the literature, it does not seem very likely that the night-time sleep improvement is caused by the improvements in motor symptoms and mood changes. Rather, it may be that DBS modulates the sleep-wake network and directly affects sleep physiology (25). It is known that STN has connections that goes beyond the motor circuits (8,18,23,26). In addition to inhibiting the anterior hypothalamus and upper mesencephalic reticular substance (22), STN reciprocally connects with the pedunculopontine tegmental nucleus, which modulates wakefulness and the REM sleep (5,7,27), and has projections on the amygdala and thalamus, which are possibly involved in sleep-wake regulation (18).

There are only a few studies available in the literature that addressed the effect of STN DBS on excessive daytime sleepiness (EDS), thus the effect of STN DBS on wakefulness remains controversial as well (8,17,27). It has been stated that EDS may either improve or worsen over time following the STN DBS therapy (17). It was reported in a recent study conducted using a nonmotor symptom assessment scale that STN DBS had a positive effect on sleep/fatigue (17). Nonetheless, EDS was not analyzed in the same study (17). There are several studies available in the literature that reported no changes in the post-operative ESS scores (8,9,17,20), and additionally it was reported in another study that the EDS remained relatively stable following the STN DBS therapy and that the night-time sleep quality improved (14). A correlation was reported in some studies (6,10) between improved EDS and reduced LED following the STN DBS therapy, as compared to other studies, in which no correlation was found between improved EDS and reduced LED (9,17,20). In comparison, in this study, similar to the findings reported in some of the aforementioned studies (6,10), a significant improvement was observed in ESS scores following the STN DBS therapy.

The effects of STN DBS on EDS may be explained by several mechanisms. First, the night-time sleep difficulties caused by deterioration of motor symptoms may cause EDS and the STN DBS therapy may reduce the EDS by improving night-time sleep quality. Secondly, the arousal systems that suffered damages due to PD in the brain (12) may be modulated by STN DBS, and this neuromodulation may contribute to the remission of PD-related sleep disorders. Thirdly, given the fact that EDS is associated with dopaminergic drugs that can induce sleep attacks (1,2,4,12,27), reduced EDS may be associated with a reduction in dopaminergic medication following DBS.

As pointed out in the literature, distinguishing the effect of reduced dopaminergic medication from the effect of DBS is difficult (29). In two studies (6,10), the dose of levodopa was sharply reduced, that is, by 90% at the 3rd month after STN DBS and by 50% at 6th month after STN DBS, respectively, following DBS. On the other hand, in this study, the mean post-operative reduction in LED was 20%, hence it was much less pronounced compared to the above-mentioned two studies with positive outcomes. The significant post-operative improvement observed in EDS in this study was a remarkable finding, considering that the dopaminergic medication was continued to be administered at high dosages. A review of the literature did not reveal any study in which the correlation between the reduced LED and the ESS scores was investigated as a means to understand whether the improvement observed in ESS scores is associated with reduced LED or with DBS. Thus, to the best of the authors’ knowledge, this study has been the first study to investigate the relation between EDS and reduced LED. In this study, no correlation was found between the reduced LED and the ESS scores, which was interpreted as a finding that indicates that the reduced daytime sleepiness is less likely to be associated with post-treatment reduction observed in LED. Additionally, there was also no correlation between the UPDRS scores and the ESS scores, which was interpreted as a finding that weakens the idea that STN DBS improves excessive daytime sleepiness by allowing better night-time sleep quality because of improved motor symptoms. Overall, these results were interpreted to mean that STN DBS leads to significant improvements in night-time sleep and reduces daytime sleepiness through the direct effect of the stimulatory electrode, independently of the motor symptoms, mood or reduction in LED. However, this hypothesis needs to be verified by further studies that utilize neuroimaging techniques to assess functional connectivity or by brain metabolism studies.

Short-term follow-up appears as a limitation in most of the studies available in the literature since optimal post-operative stimulation cannot be achieved. Thus, such studies fail to assess the balance of optimal stimulation and medical treatment, which cannot be achieved until at least 6 months after DBS (15). In comparison, in this study, all patients were evaluated at least 6 months after the STN DBS and after a mean period of eight months from the time of the STN DBS, in order to minimize the risk of sub-optimal results. Nevertheless, there were some other limitations to this study. First, a multiple sleep latency test, which would be a better option in elucidating the changes in EDS as it is an objective assessment tool, was not performed. Secondly, the study group was relatively small, which was even more of a limitation considering that the PSG recordings could be assessed in only 10 of the 26 patients, who were subjectively assessed. Thirdly, specific assessment of night-time motor symptoms could have been a more viable option than UPDRS and PDQ-39. Accordingly, it is of the belief of the authors of this study that the future studies that address night-time sleep problems would provide more useful information through a more accurate assessment of night-time PD symptoms.
CONCLUSION

The comprehensive assessment of the probable causes of the changes observed in the sleep parameters of PD patients within the scope of this study revealed that STN DBS provided a significant improvement in sleep-wake behavior by means of its neuromodulatory effects. In this context, having shed light on the effects of STN DBS on sleep quality, this study can be considered as an important contribution to the scientific literature, provided that further studies are carried out to substantiate the findings presented herein.

AUTHORSHIP CONTRIBUTION

Study conception and design: DIG, OGO
Data collection: OGO, SJ
Analysis and interpretation of results: KA, GS, OGO
Draft manuscript preparation: OGO, GS
Critical revision of the article: DIG
Other (study supervision, fundings, materials, etc...): AS, OGO

All authors (OGO, GS, SJ, KA, AS, DIG) reviewed the results and approved the final version of the manuscript.

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