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Effect of Subthalamic Nucleus Deep Brain Stimulation Treatment on Non-motor Symptoms and Sleep Quality in Parkinson's Disease Patients

Parkinson Hastalarında Subtalamik Çekirdek Derin Beyin Stimülasyonu Tedavisinin Non-motor Semptomlara ve Uyku Kalitesine Etkisi

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ABSTRACT

Aim: To evaluate the effect of subthalamic nucleus deep brain stimulation (STN-DBS) on non-motor symptoms (NMS), sleep quality, and excessive daytime sleepiness in patients with Parkinson's Disease (PD).

Method: Sixteen PD patients, who had undergone bilateral STN-DBS surgery were enrolled. The patients were assessed at the baseline and 12 months after surgery using the Unified Parkinson's Disease Rating Scale (UPDRS), Parkinson's Disease Questionnaire (PDQ-39), Beck Depression Inventory-II (BDI), Hospital Anxiety and Depression Scale (HADS), Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), and Non-Motor Symptom Questionnaire (NMS-Quest).

Results: There were significant improvements in the levodopa-equivalent daily dose, UPDRS-part-II, UPDRS-part-III, and UPDRS-part-IV at 12 months post-DBS surgery. The NMS-Quest total score at baseline was correlated with the disease duration of the patients (p=0.005 R:0.66). The PSQI score at baseline was significantly associated with a high total UPDRS and HADS score (p=0.03, p=0.004 respectively). There were no significant differences in terms of NMS-Quest total and subdomains thereof and PSQI total score and subdomains thereof, UPDRS-part I, BDI-II and HADS scores between baseline and 12 months post-DBS surgery (p>0.05 for all of them).

Conclusion: STN-DBS surgery did not change subjective sleep quality, excessive daytime sleepiness, and NMS although it improved motor symptoms, motor fluctuations, and the health-related quality of life.

Key Words: Subthalamic nucleus deep brain stimulation (STN-DBS), Sleep quality, Non-motor symptoms

ÖZET

Amaç: Parkinson Hastalığı (PH) olan hastalarda subtalamik nukleus derin beyin stimülasyonunun (STN-DBS) non- motor semptomlar (NMS), uyku kalitesi ve gündüz aşırı uykululuk üzerine etkisini değerlendirmek.

Yöntem: Bilateral STN-DBS cerrahisi geçirmiş 16 PH hastası çalışmaya alındı. Hastalar ameliyat öncesi ve ameliyattan 12 ay sonra Birleşik Parkinson Hastalığı Derecelendirme Ölçeği (BPHDÖ), Parkinson Hastalığı Anketi (PDQ-39), Beck Depresyon Envanteri-II (BDI), Hastane Anksiyete ve Depresyon Ölçeği (HADS), Pittsburgh Uyku Kalitesi İndeksi (PSQI), Epworth Uykululuk Ölçeği (ESS) ve Non-motor Semptom Anketi (NMS-Quest) kullanılarak değerlendirildi.

Bulgular: DBS ameliyatından 12 ay sonra levodopa eşdeğeri günlük dozunda, BPHDÖ-bölüm-II, BPHDÖ-bölüm-III ve BPHDÖ-bölüm-IV'te anlamlı iyileşmeler oldu. Başlangıçtaki NMS-Quest toplam puanı, hastaların hastalık süresi ile koreleydi (p=0,005 R:0,66). Başlangıçtaki PSQI skoru, yüksek BPHDÖ toplam skor ve HADS skoru ile anlamlı şekilde ilişkiliydi (sırasıyla p=0.03, p=0.004). Başlangıçtaki ve DBS cerrahisinden 12 ay sonraki NMS-Quest toplam ve alt alanları, PSQI toplam puanı ve alt alanları, BPHDÖ-bölüm-I, BDI-II ve HADS puanları arasında anlamlı fark yoktu (p>0,05 tümü için).

Sonuç: STN-DBS cerrahisi motor semptomları, motor dalgalanmaları ve sağlıkla ilişkili yaşam kalitesini iyileştirmesine rağmen gündüz aşırı uykululuk halini, subjektif uyku kalitesini ve NMS'yi değiştirmedi.

Anahtar Kelimeler: Subtalamik nukleus derin beyin stimülasyonu (STN-DBS), Uyku kalitesi, Non- semptomlar

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Introduction

Parkinson's Disease (PD) is a chronic, progressive neurodegenerative disorder, characterized by both motor symptoms and non-motor symptoms (NMS). The PD diagnosis is based on the presence of motor symptoms, including bradykinesia, rigidity, and tremor. Main NMS consist of cognitive dysfunction, psychiatric symptoms, sleep disturbances, fatigue, autonomic dysfunction, olfactory dysfunction, gastrointestinal dysfunction, and pain. NMS are very common in PD patients. Also, NMS have a more negative effect on health-related quality of life compared with motor symptoms, even in the early stages of PD (1). Sleep disorders are common NMS and have a prominent negative effect on the quality of life in PD patients. Multiple sleep disorders, such as sleep fragmentation, insomnia, REM sleep behavior disorder, excessive daytime sleepiness (EDS), periodic limb movements during sleep, and restless legs syndrome, may be seen in PD patients (2).

Subthalamic nucleus deep brain stimulation (STN-DBS) is an effective treatment, especially in PD patients with motor complications despite the best medical therapies. STN-DBS treatment effectively improves motor symptoms and quality of Life (QoL) and decreases the need for dopaminergic drugs (3). However, in the literature, there are fewer studies on the effects of STN-DBS surgery on NMS than its effects on motor symptoms. Moreover, limited available data on the effects of STN-DBS surgery on NMS, is still controversial. Some authors have reported that the total NMS burden was mitigated post-STN-DBS surgery (4-6). In contrast, some NMS such as cognitive performance, depression, suicidal attempts, impulsivity, mania, and apathy might have been worsened after STN-DBS surgery (7, 8). In addition, data on the effects of STN-DBS surgery on sleep quality and EDS, is also still contradictory. A previous study has reported improvements both in subjective sleep quality and objective sleep parameters after DBS surgery (9). Some studies have found an improvement in subjective sleep quality despite no change or deterioration in objective sleep parameters post-DBS surgery (10, 11). Although most studies have reported no changes in EDS (12-14), a few studies have demonstrated an improvement in EDS after STN-DBS surgery (15, 16). We aimed to investigate the effect of STN-DBS on NMS total and subdomains, the subjective sleep quality, and the EDS of the patients.

Material and Method

This retrospective study was approved by the University of Akdeniz Ethics Committee (KAEK-672). Sixteen advanced-stage PD patients, who had undergone bilateral STN-DBS surgery at Akdeniz University, were enrolled in this study. The indication criteria for STN-DBS surgery were the presence of a conclusive diagnosis of idiopathic PD, troublesome motor complications, including motor fluctuations or dyskinesia despite the best medical treatment and motor response to dopaminergic drugs, and the absence of uncontrolled psychiatric diseases and dementia. All surgeries were performed by the same neurosurgeon (T.U.). All patients were routinely followed by the same neurologist (N.Ş.E) during the pre-operative and post-operative periods. A week post-surgery, stimulation was turned on. During follow-ups, the stimulation settings were adjusted to provide a maximum decline in motor symptoms while avoiding the negative effects of stimulation. Informed consent forms for data collection were signed by all the patients during the visits.

Demographic information, such as sex, age, and disease duration, was collected from an electronic medical database. The patients' dopaminergic drug doses were evaluated using levodopa-equivalent daily dose (LEDD). The patients' clinical stages were assessed by a modified Hoehn and Yahr scale and the Unified Parkinson's Disease Rating Scale (UPDRS) at the baseline and follow-up visit 12 months post-DBS-surgery. UPDRS includes four parts, Part I assesses "non-motor experiences of daily life," Part II assesses "motor experiences of daily life, and Part IV assesses "motor fluctuations". Part III related to motor examination was tested under two conditions; medication-ON (Med-ON) and medication-OFF (Med-OFF) condition. Med-ON was considered as at least an hour after taking their usual levodopa dose and Med-OFF was considered as at least 12 hours without taking dopaminergic medications. At follow-up visits 12 months post-DBS surgery, the UPDRS part III was performed both under Med-ON and Med-OFF conditions when stimulation was on. The health-related quality of life of the patients was assessed with the Parkinson's Disease Questionnaire (PDQ-39), consisting of 39 items and measures "quality of life" in eight domains; mobility, stigma, activity living, communication, emotional well-being, social support, cognition, and pain. The total score ranges from 0 to 100 and a higher score indicates a poorer health-related quality of life.

The cognitive performance of the patients was performed with Mini-Mental State Examination (MMSE) scale. Montreal Cognitive Assessment (MoCA) was also used to evaluate the cognitive performance of patients. The total MoCA score ranges from 0 to 30 and a higher score shows a better cognitive function. The patients' mood was assessed with Beck Depression Inventory-II (BDI) and Hospital Anxiety and Depression Scale (HADS). BDI-II is a self-report psychometric scale, aiming to evaluate depressive symptoms. Higher global BDI-II scores indicate more severe depressive symptoms. HADS is a self-assessment scale to determine the level of depression and anxiety in a hospital medical outpatient clinic setting. It consists of 14 items, half of which are related to anxiety. Higher total HADS score shows more anxiety and depressive symptoms.

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The sleep quality of the patients was evaluated with the Pittsburgh Sleep Quality Index (PSQI) scale. It is a reliable scale that evaluates sleep quality over a 1-month term. It consists of 19 questions, including seven domains following subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction. A higher total PSQI score indicates poorer sleep quality. A PSQI total score of greater than 5 is accepted as poor sleep quality. The Epworth Sleepiness Scale (ESS) was used to evaluate EDS in the patients. The ESS requires people to rate their likelihood of falling asleep in 8 different real-life situations over the past month. The total ESS score is the sum of scores for the 8 items and ranges from 0 to 24. A higher ESS score represents greater daytime sleepiness. The ESS scores greater than 10 represent excessive daytime sleepiness.

The non-Motor Symptom Questionnaire (NMS-Quest) is a self-administered 30-item questionnaire, featuring responses as "yes," or "no," to each item with the aim of screening for the presence a wide of spectrum of NMS. A "Yes," answer indicates that the patient had experienced the problem during the previous month. NMS-Quest consists of nine different domains (gastrointestinal, urinary, sexual function, cardiovascular/falls, sleep/fatigue, mood, perceptual problems/hallucinations, attention/memory and miscellaneous symptoms including unexplained pain, olfaction, weight changes and excessive sweating). A total NMS-Quest score and an NMS-Quest subdomain score are calculated by summing 'Yes' answers indicating '1' point. An NMS-Quest total score of under 10 represents mild NMS, an NMS-Quest total score of 10 to 20 represents moderate NMS and an NMS-Quest total score of greater than 20 represents severe NMS.

Statistical Analysis: Descriptive statistics were presented as frequency, percentage, mean±standard deviation, and median (interquartile range, IQR), where appropriate. Shapiro-Wilk test, histogram and Q-Q graphics were used for evaluation of normality of distribution. Fisher's exact test was used to analyze relationships between categorical variables. For the comparison of continuous variables, Student's t-test was used when variables showed normal distribution, whereas the Mann-Whitney U test was used in the contrary case. Spearman correlation analysis was applied to determine relationships between ordinal variables or those not conforming to normal distribution. Pearson correlation test was applied to continuous variables with normal distribution. Correlation coefficients were interpreted as 0.00-0.50 = a weak correlation, 0.50 -0.70 = a moderate correlation and 0.70 – 1.00 = a strong correlation. Statistical analyses were performed by using the SPSS version 21.0 package program for Windows. P values <0.05 were accepted to show statistical significance.

Results

The pre-operative and post-operative clinical assessment results of 16 patients were analyzed in this study. Twelve patients (75%) were male. The mean age of the patients at the time of surgery was 53.5±3.6 years. The mean age of patients at the time of PD diagnosis was 42.8±3.4years. The patients had undergone DBS surgery following a mean duration of 10.4±1.4 years after PD diagnosis.

A significant decrease was seen in LEDD at 12 months post-DBS surgery (p<0.001). 12 months after DBS surgery, significant improvements were seen in terms of UPDRS-part-II, UPDRS-part-III (both med-ON and med-OFF conditions), UPDRS-part-IV, Hoehn-Yahr staging (med-OFF condition) (p<0.05 for all of them). A significant decrease was seen in PDQ-39 following DBS surgery (p=0.01). Baseline and one year post-DBS surgery scores for UPDRS-part I, BDI-II, HADS, MMSE and MoCA were not significantly different (p>0.05 for all of them). ***Table 1*** shows the clinical characteristics, mood, cognitive performance and health-related quality of life of the patients during the pre-operative period and at 12-months post-surgery follow-up.

Mean NMS-Quest total scores were 8.9±4.6 and 8.06±5.2 for baseline and after 12-months follow-up, respectively. The NMS-Quest total score at baseline was correlated with the disease duration of the patients (p=0.005; R:0.66) but not with the age, LEDD, and clinical stage of the patients (p>0.005 for all of them). There was no significant difference in the NMS-Quest total score and subdomain score at baseline and 12 months post-DBS surgery (p>0.05 for all of them). At baseline, 8 patients had mild NMS and 8 patients had moderate NMS. At 12 months follow-up post-DBS surgery, 9 patients had mild NMS and 7 patients had moderate NMS. ***Table 2*** summarizes the patients' total and subdomain scores of NMS-Quest at baseline and at 12-months follow-up post-surgery.

The mean total PSQI score was 8.06±5.2 and 6.5±4.8 at the baseline and at 12-months after surgery, respectively. Total PSQI score at the baseline was not correlated with the age, disease duration, LEDD or BDI-II score of the patients (p>0.005 for all of them). PDQI score at the baseline significantly increased with a high total UPDRS and HADS score (p=0.03, p=0.004 respectively). There were no significant differences between baseline scores and 12-months post-surgery follow-up scores for PSQI total and subdomain (p>0.05 for all of them). Nine (56.2%) patients with PSQI scores, greater than 5, had poor sleep quality prior to DBS surgery. At 12 months- follow-up after DBS-surgery, subjective sleep quality improved in 3 of 9 patients with poor sleep quality, yet two patients developed a new-onset poor sleep quality.

The mean total ESS scores at baseline and follow-up visit at 12 month post-surgery were 6.3±3.6 and 5.1±5.6, respec-

Table 1. Clinical characteristics, cognitive performance, and health-related quality of life of the patients during the pre-operative period and at follow-up 12 months post-surgery.

	Baseline mean±sd	**12-Month follow-up mean±sd**	**p**
LEDD (mg)	1697±588	1048±372	***<0.001***
UPDRS-part I	9.8±5.7	9.8±6.7	1
UPDRS-part-II	19.3±8.2	11.8±7.7	***0.01***
UPDRS-part-III (med-ON)	30.1±7.5	25.3±6.1	***0.047***
UPDRS-part-III (med-OFF)	65.8±16	43.5±15	***<0.001***
UPDRS-part-IV	11.4±3.5	4±4.2	***<0.001***
Hoehn-Yahr (med-ON)	2.4±0.3	2.5±0.4	0.3
Hoehn-Yahr (med-OFF)	3.8±0.8	2.9±0.8	**0.001**
PDQ39	42.6±21	26.5±21	***0.01***
MMSE	27.1±2.3	27.9±2.3	0.17
MoCA	21.5±4	22±4.8	0.5
BDI-II	12.4±6.4	12.1±9.5	0.9
HADS	12.5±6.9	10.5±7.5	0.1

LEDD: levodopa-equivalent daily dose, UPDRS: Unified Parkinson's Disease Rating Scale, PDQ-39: Parkinson's Disease Questionnaire, MMSE: Mini-Mental State Examination, MoCA: Montreal Cognitive, BDI-II; Beck Depression Inventory-II, HADS; Hospital Anxiety and Depression Scale

Table 2. The patients' total and subdomain scores of NMS-Quest, during the pre-operative period and at 12-month follow-up post-surgery.

	Baseline mean±sd (min-max)	**12-Month follow-up mean±sd (min-max)**	**p**
NMS-Quest total score	8.9±4.6 (2-15)	8.06±5.2 (0-15)	0.5
Gastrointestinal	1.6±1.5 (0-5)	1.5±1.3 (0-4)	0.9
Urinary	1.5±0.6 (1-2)	1.2±0.85 (0-2)	0.96
Sexual function	0.81±0.83(0-2)	0.75±0.93 (0-2)	0.77
Cardiovascular/falls	0.5±0.51 (0-1)	0.56±0.72 (0-2)	0.75
Sleep/fatigue	1.6±1.4 (0-3)	1.6±1.3 (0-5)	1
Mood	0.56±0.8 (0-1)	0.5±0.73 (0-1)	0.75
Perceptual problems/ hallucinations	0.12 ±0.34 (0-1)	0.6±0.25 (0-O)	0.33
Attention/memory	0.81±0.91 (0-2)	0.56±0.72 (0-2)	0.38
Miscellaneous symptoms	1.3±0.9 (0-2)	1.1±1.04 (0-3)	0.66

NMS-Quest; non-Motor Symptom Questionnaire

tively. The baseline ESS score was not correlated with the patients' age, disease duration, LEDD, BDI-II, HADS, or total UPDRS scores (p>0.05 for all of them). There were no significant differences between ESS total score at baseline and at follow-up visits 12 months post-DBS surgery (p=0.45). EDS had been observed in 2 patients prior to DBS surgery. At follow-up visits 12 months post-surgery, EDS improved in one patient, yet 3 patients developed new-onset EDS. Table 3 summarizes the patients' PSQI total, subdomain, and ESS scores at baseline and 12 months after surgery.

Discussion

The present study evaluated the effect of STN-DBS treatment on sleep quality and non-motor symptoms in PD patients. The present study demonstrated that STN-DBS

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Table 3. The patients' PSQI total and subdomain scores and ESS scores during the pre-operative period and 12-month follow-up post-surgery.

	Baseline mean±sd	12-Month follow-up mean±sd	p
PSQI total score	8.06±5.2	6.5±4.8	0.2
Subjective sleep quality	1.4±0.9	1.25±0.9	0.5
Sleep latency	1.5±1.1	1.3±1.2	0.5
Sleep duration	1.3±1.1	0.93±1.06	0.1
Habitual sleep efficiency	0.81±1.2	0.62±1.02	0.3
Sleep disturbances	1.75±0.6	1.37±0.8	0.1
Use of sleeping medication	0.37±1.02	0.12±0.5	0.4
Daytime dysfunction	1.06±0.77	0.87±1.02	0.4
ESS total score	6.3±3.6	5.1±5.6	0.45

PSQI: Pittsburgh Sleep Quality Index, ESS: Epworth Sleepiness Scale

improved motor symptoms, levodopa-induced motor complications, and health-related quality of life as indicated in previous studies (3, 8).

In this study, NMS was found to be correlated only with the disease duration. We found that NMS, as assessed with UPDRS Part-I, total NMS-Quest and subdomain scores, were not improved with STN-DBS surgery. In the literature, there are conflicting results on the effects of STN-DBS surgery on NMS. A previous study, assessing NMS with NMS-Quest, has found an improvement in total NMS burden at 12 months post-surgery, which was in correlation with improvements in health-related quality of life (4). A 36-month follow-up study has demonstrated that STN-DBS surgery significantly improved total NMS burden and specific NMS, such as sleep/fatigue, urinary symptoms, olfactory functions and pain (5). A recent meta-analysis reported that bilateral STN-DBS therapy significantly reduced total NMS and subdomain scores, including sleep, miscellaneous, urinary, sexual and attention/memory (6). A study has reported that STN-DBS improved some of the NMS domains, such as sleep disturbance, yet worsened cognitive performance, such as verbal fluency and executive function (8). Also, other neuropsychiatric symptoms, such as depression, suicidal attempts, impulsivity, mania and apathy may worsen following STN-DBS surgery (7). In the present study, depression and anxiety symptoms did not change following STN-DBS surgery.

Poor sleep quality was very common in our patients both before and after DBS surgery. We found an association between anxiety symptoms and sleep quality in patients. Also, there was an association between poor sleep quality and high total UPDRS scores. However, despite a significant improvement in total UPDRS scores, STN-DBS treatment did not change PSQI total and subdomain scores. In the literature, there are different results for the effect of STN-DBS therapy on sleep quality. A previous study has found that subjective and objective sleep clinical outcomes improved 6 months after DBS surgery in PD patients (9). Most studies have shown an improvement of the total PSQI score subsequent to STN-DBS surgery (17-19). In contrast, Torun, et al., have shown no significant changes in the total PSQI scores, despite an improvement in the subscore of PSQI, including subjective sleep latency and sleep duration at 3 months post-STN-DBS (20). A meta-analysis, including 30 studies, has demonstrated that in the 6-month follow-up period, STN-DBS treatment improved subjective sleep quality, but did not change most PSG parameters, including sleep efficiency and sleep architecture (10). It has been reported that the improvement in subjective sleep quality could be explained by the improvement in nocturnal mobility, particularly in the early periods after surgery (21). Previous studies have reported a significant association between subjective sleep quality and mood, particularly depression (11, 12). Dulski, et al., have reported that the reason for the improvement in subjective sleep quality despite the worsening of objective sleep parameters at 6 months post-STN-DBS surgery, could be explained by the improvement in mood. They have also shown that at 12 months post-DBS surgery, in parallel to mood deterioration, all subjective sleep quality measures and other non-motor symptoms (especially cardiovascular, gastrointestinal, fatigue and sexual symptoms) were worse than 6 month follow-up visits (11). Therefore, it has been considered that the change in mood due to the placebo effect of the surgery could have a direct effect on subjective sleep quality (21). In this study, no changes in both mood and subjective sleep quality were observed at 12 months post-DBS surgery.

The present study found no correlation between the ESS score at baseline and the age, disease duration, and clinical characteristics of the patients. We showed that total ESS score did not significantly change post-DBS surgery. Also, we observed that EDS worsened in three patients and improved in only one patient post-DBS surgery. In the literature, there are a few studies demonstrating an improvement in the EDS following STN-DBS surgery (15, 16, 22). In contrast, most studies have shown that STN-DBS treatment did not change total ESS scores, despite reductions in dopaminergic drugs as in our study (11-14, 23, 24). Moreover, previous studies have reported no correlation between reduction in dopaminergic medication and changes in ESS scores post-DBS surgery (13, 14). A recent meta analyze including 30 studies also reported that the improvement in excessive daytime sleepiness in the patients did not persist for one year after DBS surgery (10). Multiple factors, including advanced stage, comorbid sleep disorder, the use of anti-Parkinson medication and neurodegeneration of the regions such as the hypothalamus and various brainstem nuclei, responsible for sleep-wake regulation, may have a contribution in EDS in PD patients. We think that the presence of new-onset EDS in our population at 12-month follow-up, could be related to the progression of the disease.

Limitations: This study had several limitations. A major limitation is the small number of patients. The other important limitation is that it was impossible to evaluate the patients' sleep parameters with objective parameters such as PSG. Also, NMS subdomains could not be assessed with objective measures. We did not investigate the effect of STN-DBS surgery on NMS during early post-operative period. The progression of the disease during the 12 months post-surgery may affect the results. Despite these limitations, this study demonstrated, in contrast with most previous studies in the literature, that STN-DBS treatment did not improve NMS, EDS, and sleep quality.

Conclusion: In conclusion, despite improvements in motor symptoms, motor fluctuations and the health-related quality of life, STN-DBS treatment had no beneficial long-term effect on subjective sleep quality, EDS and NMS.

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