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The Influence of Subthalamic Nucleus Deep Brain Stimulation on Physical, Emotional, Cognitive Functions and Daily Living Activities in Patients with Parkinson's Disease

Parkinson Hastalarında Subtalamik Çekirdek Derin Beyin Stimülasyonunun Fiziksel, Emosyonel, Kognitif Fonksiyon ve Günlük Yaşam Aktiviteleri Üzerine Etkisi

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ABSTRACT

AIM: To describe effectiveness of deep brain stimulation of subthalamic nucleus (DBS STN) on physical, emotional, cognitive functions and daily activities in Parkinson's patients.

MATERIAL and METHODS: Ten patients (51.20 ±10.20 yr.) were assessed three times. The Time Up and Go Test, 12 m Walking Test and Chair Stand Test were used to assess mobility and balance. Purdeu Pegboard and hand writing tests were used to evaluate hand function. The Hospital Anxiety and Depression Scale (HAD) was used to detect depressive symptoms and anxiety score. The Unified Parkinson\'s Disease Rating Scale (UPDRS) and Hoehn &Yahr Scale were also used. The Schwab and England Test was used to evaluate the daily activities (ADL).

RESULTS: The results showed that all the patients' mobility and balance ability improved after surgery ($p<0.05$). Depressive symptoms / anxiety scores were found to be lower than before surgery ($p<0.05$). There were differences in terms of ADL and UPDRS scores after surgery ($p<0.05$). At six month after surgery; depressive symptoms decreased by 78%. ADL and UPDRS motor and total scores improved by 190%, 72%, and 78% respectively.

CONCLUSION: STN DBS is an effective treatment to improve physical functioning, emotional status and daily activities in Parkinson's patients. However, it did not show any positive effect on cognitive function.

KEYWORDS: Parkinson's disease, Subthalamic nucleus, Balance, Mobility, Emotional status, Daily living activities

ÖZ

AMAÇ: Parkinson hastalarında Subtalamik Çekirdek Derin Beyin Stimülasyon'un (STN DBS) fiziksel, emosyonel, kognitif fonksiyon ve günlük yaşam aktiviteleri üzerine etkilerini değerlendirmek.

YÖNTEM ve GEREÇ: STN DBS cerrahisi uygulanan 10 hasta cerrahi öncesi, cerrahi sonrası 3. ve 6. ayda değerlendirilmiştir. Mobilite ve denge yeteneği Süreli Kalk Yürü Testi, 12 m Yürüme Testi, Otur-Kalk Testi ile el fonksiyonları Purdue Pegboard Testi ve el ile yazı yazma testleri ile ve emosyonel statü Hastane Anksiyete ve Depresyon Ölçeği (HAD) ile değerlendirilmiştir. Parkinson hastalığının klinik şiddetini belirlemek için Birleşik Parkinson Hastalığı Değerlendirme Ölçeği (BPHDÖ), evreyi belirlemede Hoehn&Yahr Ölçeği, günlük yaşam aktivitelerinin (GYA) değerlendirilmesinde Schwab ve England GYA ölçeği kullanılmıştır.

BULGULAR: Olguların yaş ortalaması 51,20 ±10,20 yıldır. Sonuçta mobilite ve denge yeteneği test sonuçlarında cerrahi sonrasında anlamlı gelişmeler elde edilmiştir ($p<0.05$). Depresyon / anksiyete skorları cerrahi öncesine göre daha düşük bulunmuştur ($p<0.05$). Cerrahi sonrasında GYA ve BPHDÖ skorları arasında istatistiksel anlamlı farklılık bulunmuştur ($p<0.05$). Tedavinin etkinliği açısından incelendiğinde cerrahi sonrası 6. ayda depresif semptomlarda %78 azalma, GYA %190, BPHDÖ motor bulgularda %72, BPHDÖ toplam skorda %78 oranında gelişme elde edilmiştir.

SONUÇ: STN DBS cerrahisinin parkinson hastalarında fiziksel fonksiyon, emosyonel statü ve GYA üzerine iyileştirici yönde etkileri olduğunu, fakat kognitif fonksiyonlar üzerine etkisi olmadığını göstermiştir.

ANAHTAR SÖZCÜKLER: Parkinson hastalığı, Subtalamik çekirdek, Denge, Mobilite, Emosyonel statü, Günlük yaşam aktiviteleri

INTRODUCTION

Parkinson's disease (PD) is a progressive movement disorder ensuing from dopaminergic depletion of the basal ganglia, substantia nigra pars compacta. The resulting disruption of the motor circuit that connects the basal ganglia to the motor cortex leads to the clinical manifestations of tremor, rigidity, bradykinesia and postural instability. The management of Parkinson's disease is mainly pharmacological. Levodopa and dopamine agonists are able to provide adequate symptomatic control in the first 5–10 years of therapy. However, long-term evolution is marred in the majority of patients by complications, such as fluctuations in the motor state and dyskinesias (16, 19). In recent years, surgery has been revitalized for the treatment of patients with uncontrollable motor complications. The aim of surgery is mainly to decrease the pathological influences of abnormal neuronal drive from the subthalamic nucleus (STN) that characterize the Parkinsonian state. Deep brain stimulation (DBS) mimics the effect of lesions (thalamotomy, pallidotomy, etc.) with less risk of permanent neurological deficits (11). Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective treatment to improve motor function, daily living activities and emotional status in patients with advanced Parkinson's disease. STN DBS, however, fails to address numerous symptoms that are disabling in advanced PD, such as levodopa-refractory axial motor disturbances. Several studies have shown a substantial beneficial effect of DBS of the STN in advanced Parkinson's disease 12–24 months post-operatively (13, 17, 23). The other studies with respect to short- and long-term efficacy of STN-DBS have shown marked improvements in motor function as well as a reduction of antiparkinsonian drug treatment. Similar results have been reported in a smaller number of patients by a few other groups (8, 23). The aim of this study was to describe the effects of deep brain stimulation of subthalamic nucleus (DBS STN) on physical, emotional, cognitive functions and daily living activities in patients with Parkinson's disease.

MATERIAL and METHODS

Patient Group

We studied 10 (5 male-5 female) consecutive patients who underwent bilateral stimulation of the subthalamic nucleus between January 2008 and January 2010. The selection criteria were clinically diagnosed Parkinson's disease, severe levodopa-related motor complications despite optimal adjustment of antiparkinsonian medication, no surgical contraindications, no dementia or major ongoing psychiatric illness and no other neurological disorders. The ethics committee of Pamukkale University in Turkey approved the study, and all the patients gave their written informed consent. The characteristics of the patients are summarized in Table I.

Surgery Procedure

All STN DBS procedures were performed by one neurosurgeon in two stages: (1) insertion of bilateral electrodes under local anaesthesia using microelectrode recording, and (2) connection of the electrodes to pulse generators under general anaesthesia, performed approximately 1 day after lead placement. The operative technique was described in details elsewhere (5). The subthalamic nuclei were localized stereotactically by magnetic resonance imaging (MRI), and microelectrode recordings were performed to define STN. The quadripolar electrodes (Medtronic 37601 Activa PC) were implanted bilaterally in all patients. Surgery was performed with local anesthesia and clinical effect on rigidity and tremor was tested under stimulation using a macroelectrode. All patients underwent MRI postoperatively for the assessment of surgical complications. A programmable pulse generator was implanted subcutaneously under general anesthesia on the second day after implantation of the electrodes. Stimulation settings and medication were progressively adjusted.

Clinical Assessment

Patients were evaluated preoperatively and postoperatively at third and sixth months. Unblinded assessments were performed when patients had taken no medication for 8 to 12 hours (off medication) and during periods of maximal clinical benefit after the administration of a dose of liquid levodopa that was 50 percent higher than the usual morning dose of dopaminergic treatment (on medication). Postoperatively, patients were assessed during stimulation.

Outcome Measures

The physical therapist assessed the patient with clinical performance tests, and the same PT assessed all patients in all test situations.

The Timed Up & Go (TUG)

The subject sits in an armchair (seat height of 46 cm) with the back against the chair and arms resting on the chair's arms. The instruction "Go" initiates the subject to stand up and walk at a comfortable pace to a line 3 meters away, where both feet should pass the line before the subject turns around and walks back to sit down again. Timing commences when the subject's back is leaving the back of the chair, and stops when the buttock reaches the seat of the chair. Average time required to complete the test TUG is reported (7).

Chair-Stand Test

The time required to stand up from a chair and to sit down five times consecutively as fast as possible is registered. The subject sits in an armchair (seat height of 46 cm) with the back against the chair, and with arms folded across the chest. The subject's regular footwear is worn. The test begins with the commando "Start now". Timing commence when the subject's back is leaving the back of the chair, and stops when the subject's buttock reaches the seat for the fifth time. One trial is performed. The average time required to complete the test is reported (7).

12 Meters Walking Test

The subject is standing still and then walks at a comfortable (preferred) speed straight forward. The subject's regular

footwear is used. Timing commences after the command "Go" and stops when the subject passes the mark for twelve meters. One trial is performed. The average time required to complete the test time is reported (7).

Unified Parkinson's Disease Rating Scale (UPDRS)

Patients were clinically assessed using the UPDRS. Different scores were extracted from this scale: the psychological status (items 1 and 4 of the UPDRS I), the daily living activities (ADL) score (items 5 and 17 of the UPDRS II), the motor score (items 18–31 of the UPDRS III), the dyskinesias score (items 32–35 of the UPDRS IV), the total UPDRS score comprised between 0 and 108, and the worst value was 108 (6).

Hoehn&Yahr Scale (H&Y)

H&Y is a commonly used system for describing how the symptoms of PD progress. The H&Y original scale included stages 1 through 5 with Stage 0: no signs of disease, stage 1: unilateral symptoms only, stage 2: bilateral symptoms and impairment of balance, stage 3: balance impairment, mild to moderate disease and physically independent, stage 4: severe disability, but still able to walk or stand unassisted, stage 5: needing a wheelchair or bedridden unless assisted (6).

Schwab and England Daily Living Activities Test (ADL)

The Schwab and England Test was used to evaluate the daily living activities (ADL). The test rates the patient's ability to perform ADL from 100% (essentially normal) to 0% (vegetative) (6).

Purdeu Pegboard Test

The Purdue Pegboard test measures dexterity for two types of activity: one, involving the gross movement of arms, hands, and fingers and the other in primarily fingertip dexterity. The test consists of four parts: right hand, left hand, both hands and assembly. Their total is counted (20).

Hand Writing Tests

The sentence was selected and the writing task was performed using by dominant hand. Average time required to complete the test is reported.

Hospital Anxiety and Depression Scale (HAD)

HAD was applied to detect depressive symptoms and to describe anxiety score (10).

Hodkinson Abbreviated Mental Test (AMT)

Cognitive performance was measured with AMT. AMT consisting of 10 questions to test time and place, orientation, memory and arithmetic skills (1).

All participants gave informed consent and the study was approved by the ethical board committee of Pamukkale University Medical Faculty (Ref no: 67 date, 03.04.2009). This study was supported by the Pamukkale University Scientific Research Projects Foundation (Ref no:2009SBE003).

Statistical Analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS version 13.0). The Wilcoxon rank sum test was applied for comparison between the mean scores preoperatively and at the postoperative assessment. The effects of bilateral STN DBS on UPDRS, H&Y, ADL, HAD, AMT, hand function, mobility and balance assessment tests were analyzed using the paired t- test. A level of $p<0.05$ was considered significant.

RESULTS

The demographics and clinical characteristics of patients at baseline are shown in Table I. The results of this study showed that all the patients' mobility and balance ability significantly improved at the third month and sixth month after surgery ($p<0.05$). The mobility and balance assessment values at the baseline, third month and sixth month are shown in Table II.

The hand function tests were significantly improved between the three assessments. Post hoc comparisons revealed that the comparison between preoperative and third month ($p<0.05$) and sixth month ($p<0.05$) were significant. The hand function tests are shown in Table III.

The anxiety and depression scores of thought disorders significantly decreased with month ($p<0.05$). Post hoc anxiety scores comparison revealed that differences were significant between before surgery and third month after surgery ($P=0.000$) and between before surgery and sixth month postop ($P=0.003$). Depressive symptoms score was found to be lower after surgery than before surgery ($p<0.05$). Compared to the preoperative period, third month and sixth month mental status scores were not significantly different ($p>0.05$). Mood status score and mental status score are shown in Table IV.

Compared to the preoperative baseline, third month and sixth month score; the UPDRS-I, II, III, and IV scores in both the 'on' and 'off' states were significantly better ($p<0.05$). All aspects of the motor symptoms including speech, tremor, rigidity, and postural stability were significantly improved after surgery ($p<0.05$). Compared to the preoperative, third month and sixth month; the ADL scores were significantly better ($p<0.05$). At 6 months after surgery, the ADL score was increased from 20.60 ± 1.64 to 60.83 ± 2.85 (Paired t-test) ($p<0.05$). H&Y score was decreased from 4.20 ± 0.63 to 2.33 ± 1.50 at sixth month postop. Levodopa equivalents intake (LED) was reduced from a mean of 445.00 ± 369.27 to 208.33 ± 281.36 mg/day after six months. Compared to the preoperative, third month and sixth month; the UPDRS total scores were significantly improved ($p=0.000$) (Table V).

DISCUSSION

In patients with advanced Parkinson's disease who were followed prospectively, six month bilateral stimulation of the subthalamic nucleus led to significant postoperative improvements in all parkinsonian motor signs that were assessed. STN DBS is superior to best medical therapy in

improving motor function, emotional status and daily living activities in PD patients with motor complications. The improvements over baseline were sustained six months after surgery (14). STN stimulation has consistently been shown to attenuate the motor symptoms of PD and to decrease the daily dosage of medication, thus reducing drug related motor complications and according to some reports (3). Rodriguez Oroz et al., found that STN stimulation daily dosage of levodopa was significantly reduced (P<0.001) (18). In our results, LED was reduced from a mean of 445.00 ± 369.27 to 208.33 ± 281.36 mg/day after six months.

Postural instability is one of the cardinal symptoms of Parkinson's disease (PD), and persons with PD have an increased risk of falling. Most falls occur during functional activities, e.g. walking and turning (12). STN DBS provides significant motor

Table I: Demographic Characteristics of Patients Included in Study

	Min-Max	X±SD
Age (yr)	31.00 – 62.00	51.20 ± 10.20
Height (cm)	150 – 170	164 ± 0.06
Weight (kg)	47.00 – 104. 00	67.30 ± 17.99
BMI (Kg/m^2)	17.72 – 35.99	24.75 ± 5.66
Duration of disease (yr)	9.00 – 25.00	13.40 ± 5.12
Duration of using levodopa (yr)	9.00 – 25.00	12.50 ± 5.14
Equivalent daily dose of levodopa (mg)	0 – 1000	445.00 ± 369. 27

Table II: Mobility and Balance Assessment

				P- Value		
	Preop (N=10)	Postop 3rd month (N=10)	Postop 6th month (N=6)	Preop – postop 3rd month	Preop - postop 6th month	Postop 3rd – 6th month
Timed Up&Go Test (sec)	43.20 ± 22.38	19.90 ± 21.46	27.00 ± 32.21	P=0.008*	P=0.043*	P=0.157
Chair-Stand Test (Repetition/30sn)	4.60 ± 12.09	9.50 ± 4.35	11.16 ± 8.47	P=0.003*	P=0.037*	P=0.807
12m Walking Test (sec)	72.90 ± 37.50	21.80 ± 28.56	18.50 ± 16.93	P=0.002*	P=0.028*	P=0.417

* *Paired t- test.*

Table III: Assessment of Hand Function

				P- Value		
	Preop (N=10)	Postop 3rd month (N=10)	Postop 6th month (N=6)	Preop - postop 3rd month	Preop - postop 6th month	Postop 3rd – 6th month
Purdeu Pegboard Test						
Right hand	5.30 ± 3.65	10.20 ± 2.65	8.66 ± 3.98	P=0.000*	P=0.090	P=0.112
Left hand	5.50 ± 3.68	9.80 ±3.35	9.16 ± 5.26	P=0.000*	P=0.036*	P=0.235
Both hands	4.30 ± 3.02	7.30 ± 3.23	6.16 ± 4.49	P=0.000*	P=0.074	P=0.130
Assembly	2.70 ± 1.56	5.80 ± 2.29	4.66 ± 3.20	P=0.000*	P=0.027*	P=0.058
Hand Writing Tests	52.70 ± 29.45	41.80 ± 28.35	64.33 ± 57.40	P=0.036*	P=0.290	P=0.083

* *Paired t- test.*

benefits for patients with advanced Parkinson's disease, while reducing dyskinesia and motor fluctuations. Several study shows that 12 months follow-up after stimulation resulted in improved scores for akinesia, rigidity, tremor, impairment of arising from chair, gait and postural instability, when patients were evaluated off in the medication and on medication state (15). Kelly investigated the effects of unilateral and bilateral subthalamic nucleus stimulation on gait and mobility in PD. They found that bilateral and unilateral STN DBS was effective on mobility and gait function (7). According to our results, mobility and balance ability significantly improved at three months and six months after surgery (P<0.05). Several studies have demonstrated significant improvement of bradykinesia, rigidity, hand function in PD after bilateral STN DBS. Tabbal et al. found that STN DBS reduces rigidity (P<0.05) with a 25 – 83% decrease in UPDRS bradykinesia ratings with bilateral

Table IV: Assessment of Mood Status and Mental Status

				P- Value		
	Preop (N=10)	Postop 3rd month (N=10)	Postop 6th month (N=6)	Preop - postop 3rd month	Preop - postop 6th month	Postop 3rd – 6th month
HAD						
Anxiety status	16.60 ± 4.62	4.40 ± 3.94	4.83 ±2.04	P=0.000*	P=0.003*	P=0.165
Depression status	13.60 ± 6.48	4.40 ± 2.54	2.83 ± 2.48	P=0.001*	P=0.052	P=0.490
Mental Status	8.60 ± 1.42	8.80 ± 1.87	8.50 ± 1.22	P=0.509	P=0.661	P=0.695

* *Paired t- test.*

Table V: Assessment of Parkinsonian Symptoms

				P- Value		
	Preop (N=10)	Postop 3rd month (N=10)	Postop 6th month (N=6)	Preop - postop 3rd month	Preop - postop 6th month	Postop 3rd – 6th month
ADL	20.60 ± 1.64	60.40 ± 2.79	60.83 ± 2.85	P=0.000*	P=0.001*	P=0.341
H&Y	4.20 ± 0.63	2.80 ± 0.91	2.33 ± 1.50	P=0.000*	P=0.020*	P=0.741
UPDRS						
Mood status (Part I)	4.60 ± 3.50	2.50 ± 3.06	1.33 ± 2.33	P=0.016*	P=0.007*	P=0.175
ADL(on) (Part II)	27.10 ± 13.80	9.80 ± 5.78	18.50 ± 10.59	P=0.000*	P=0.050*	P=0.629
ADL(off) (Part II)	37.10 ± 9.82	15.00 ± 9.74	15.66 ± 9.66	P=0.000*	P=0.002*	P=0.092
Motor scores(Part III)	35.40 ± 13.92	11.80 ± 10.70	9.50 ± 10.25	P=0.000*	P=0.000*	P=0.517
Speech	2.70 ± 1.15	1.10 ± 0.99	0.83 ± 0.75	P=0.001*	P=0.011*	P=0.175
Tremor	2.80 ± 1.47	0.80 ± 0.91	0.33 ± 0.51	P=0.000*	P=0.002*	P=0.076
Rigidity	2.50 ± 0.40	0.70 ± 0.30	0.33 ± 0.51	P=0.001*	P=0.003*	P=0.465
Postural stability	2.10 ± 1.10	0.90 ± 0.99	0.16 ± 0.40	P=0.000*	P=0.001*	P=0.076
UPDRS Diskinesias (Part IV)	9.40 ± 1.64	2.10 ± 2.28	3.16 ± 3.37	P=0.000*	P=0.003*	P=0.045*
UPDRS total	120.70 ± 39.42	41.80 ± 28.54	25.33 ± 20.23	P=0.000*	P=0.000*	P=0.657
Daily L-dopa (mg)	445.00 ± 369. 27	235.00 ± 331. 49	208.33 ± 281. 36	P=0.028*	P=0.356	P=0.419

* *Paired t- test.*

STN DBS, and the performance on the Purdue Pegboard test improved by 75% (21). We have found that the Purdeu Pegboard test score and hand writing test score significantly improved after postoperative six months (P<0.05).

The mood strongly affects the functional status of patients with a chronic disease. Depression is a frequent complication of PD. Wang et al. stated that the Self-Rating Depression Scale scores decreased notably within 6 months postoperatively (P<0.05), and the Hamilton Rating Scale for Depression scores decreased notably within 3 months postoperatively (P<0.05) while in the STN- DBS group, the correlation between the UPDRS-III and SDS scores was significant at 3 months and 6 months postoperatively (24). These results imply that the improvement in the motor symptoms caused by the STN–DBS relieved the depressive mood of PD patients remarkably in the short term. Similar results are explained by Martinez-Martin et al. (12). Our results are similar to with literature. In the present literature, the effects of STN DBS on cognitive functions and behaviors is not well known. Comparisons between preoperative and postoperative (from 3 to 12 months after surgery) evaluations have shown minor improvements in frontal lobe function. On the other hand, preoperative scores between one year and three years after surgery is not significantly better (4). In this study, the AMT score was not significantly different at six months after surgery.

DBS (STN-S) is an effective treatment for functional capacity in PD. The Schwab and England scale has been used in other studies to assess the effects of surgical treatment in patients with PD in both the on-medication and off-medication states. Deep-brain stimulation of the thalamus has resulted in long-term improvement in tremor and activities of daily living. In the STN-S group, all disability indicated that improvement at twelfth month as measured by a decrease in the UPDRS-ADL score of 52% (p<0.001) with respect to the preoperative value. The FIM score increased after surgery by about 8% from baseline (2). In another study, the patients' scores at five years for motor function while off medication improved by 54% compared with the baseline (P<0.001) and those for activities of daily living improved by 49% (P<0.001) (9). Tir et al. reported a decrease by 43% in the Unified Parkinson's Disease Rating Scale Part III score twelve months after surgery while the Unified Parkinson's Disease Rating Scale Part II score (activities of daily living) decreased by 34%, and the severity of dyskinesia-related disability decreased by 61% (22). Our results are in line with the literature. UPDRS scores significantly decreased six months after surgery. Speech, tremor, rigidity and postural stability were significantly improved after surgery (p<0.05). At 6 months after surgery, the ADL score was increased from 20.60±1.64 to 60.83±2.85 (p<0.05). The H&Y score and LED were significantly decreased after six months (p<0.05). Depressive symptoms decreased by 78% six months after surgery. ADL and UPDRS motor and total scores improved by 190%, 72%, 78% respectively.

CONCLUSION

Our study shows that selected patients with advanced PD benefit significantly from chronic STN neuromodulation, with consistent and stable improvements in motor physical, emotional and daily living activities in patients with PD. Cognitive function remained unchanged after STN surgery.

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