EREDETI KÖZLEMÉNY

ORIGINAL ARTICLE

Effects of the combined treatment of bilateral subthalamic nucleus stimulation and levodopa on balance and mobility in Parkinson's disease

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Background and purpose – To evaluate the efficacy of the combined therapy of bilateral subthalamic nucleus deep brain stimulation (STN-DBS) and dopaminergic medication on balance and mobility in patients with Parkinson's disease (PD).
Methods – Eighteen PD patients under bilateral STN-DBS stimulation therapy, were enrolled in this study. Unified Parkinson's Disease Rating Scale (UPDRS) was applied to assess the patients' clinical characteristics. UPDRS part III postural instability/gait disorder (PIGD) scores (sum of items 3.9-3.13) and UPDRS part III postural stability item (item 3.12) were calculated separately. Patients were evaluated with Berg Balance Scale (BBS), Mini-Balance Evaluation Systems Test (Mini-BESTest), Timed Up and Go (TUG) test, dual-task TUG test, and Forward Functional Reach (FFR) Test in two conditions: Stimulation-ON (stim-ON)/Medication-ON (Med-ON) and Stimulation-OFF (Stim-OFF)/Med-ON
Results – The mean age of patients was 59.5±9.1 (R: 41-71) years. The UPDRS part III total score and PIGD subsection score significantly improved after stimulation (p=0.001), but the postural instability item of the UPDRS part III did not change significantly (p=0.1). There were no significant differences between the Stim-ON/Med-ON and Stim-OFF/Med-ON conditions, in terms of total Mini-BESTest total scores, total BBS score, FFR test score (p>0.05 for all of them).

A kombinált kétoldali subthalamicusmag-stimuláció és levodopakezelés hatása az egyensúlyra és a mobilitásra Parkinson-kórban
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Háttér és cél – A kétoldali subthalamicus mag mély agyi stimulációja (STN-DBS) és a dopaminerg gyógyszeres kezelés együttes hatékonyságának értékelése az egyensúlyra és a mobilitásra Parkinson-kórban (PD) szenvedő betegeknél.
Módszerek – A vizsgálatba 18, kétoldali STN-DBS stimulációs terápia alatt álló PD-beteget vontak be. A betegek klinikai jellemzőinek értékelésére az egységes Parkinson-kór értékelő skálát (UPDRS) alkalmazták. Az UPDRS III. részének posturalis instabilitás/járási rendellenesség- (PIGD-) pontszámát (a 3.9–3.13. tételek összege) és az UPDRS III. részének posturalis stabilitási tételét (3.12. tétel) külön-külön számították ki. A betegeket Berg-féle egyensúlyskálával (BBS), Mini egyensúly-értékelő rendszer Teszttel (Mini-BESTest), Timed Up and Go (TUG) teszttel, kettős feladatú TUG teszttel és Forward Functional Reach (FFR) teszttel értékelték két állapot szerint: Stimuláció-ON (stim-ON)/gyógyszer-ON (Med-ON) és Stimuláció-OFF (Stim-OFF)/Med-ON.
Eredmények – A betegek átlagéletkora 59,5 ± 9,1 (R: 41–71) év volt. Az UPDRS III. részének összpontszáma és a PIGD alszekció pontszáma szignifikánsan javult a stimulációt követően (p = 0,001), de az UPDRS III. részének posturalis instabilitás tétele nem változott szignifikánsan (p = 0,1). A Stim-ON/Med-ON és Stim-OFF/Med-ON körülmények között nem volt szignifikáns különbség a Mini-BESTest-összpontszám,

TUG test was significantly improved in the Stim-ON/Med-ON condition compared to Stim-OFF/Med-ON condition (p=0.03), but DT-TUG test did not change (p=0.1).
Conclusion – Combined bilateral STN-DBS and dopaminergic medication therapy had an additional improvement on motor symptoms and mobility performance, but not on balance and dual-task mobility.

Keywords: Parkinson's disease, balance, mobility, bilateral chronic subthalamic nucleus stimulation, levodopa

a BBS-összpontszám, az FFR teszt pontszámai között (p > 0,05 mindegyiknél).
A TUG teszt szignifikánsan javult a Stim-ON/Med-ON állapotban a Stim-OFF/Med-ON állapothoz képest (p = 0,03), de a DT-TUG teszt nem változott (p = 0,1).
Következtetés – A kombinált kétoldali STN-DBS és dopaminerg terápia további javulást eredményezett a motoros tünetek és a mobilitási teljesítmény tekintetében, de az egyensúly és a kettős feladatú mobilitás tekintetében nem.

Kulcsszavak: Parkinson-kór, egyensúly, mobilitás, kétoldali krónikus subthalamusmag-stimuláció, levodopa

Axial motor symptoms including gait impairment and postural instability are common and severe problems in patients with Parkinson's disease (PD). Postural instability and gait impairment may lead to falls and injuries and these are common reasons for physical disability in PD. Gait impairments in PD consist of the reduction in stride length, asymmetric loss of swing of the arms, an abnormal "stooped" posture, "freezing of gait (FOG)", and festination[1]. In PD, postural dysfunction can occur in four main postural control systems; balance during quiet stance, reactive postural adjustments to external perturbations, anticipatory postural adjustments in preparation for voluntary movements, and dynamic balance during movements such as walking[2]. Postural instability and gait impairment responses to dopaminergic medications and subthalamic nucleus deep brain stimulation (STN-DBS), used in the treatment of Parkinson's disease (PD), vary[1–3].

Deep brain stimulation (DBS) is an effective treatment for the improvement of motor symptoms in patients with PD, who have problematic motor fluctuations and dyskinesia, which are refractory to the best medical therapy. Previous studies have reported that in patients with advanced PD, DBS was more effective than best medical therapy in improving motor symptoms, including such as tremors, rigidity, bradykinesia, and quality of life (QoL)[4, 5]. While the efficacy of DBS on motor symptoms is well demonstrated, the effects of DBS on gait impairment and postural abnormalities remain controversial. Some prospective studies have reported that both STN stimulation and globus pallidus internus (GPi) stimulation significantly improved the postural instability and gait difficulty during the first year after DBS surgery, with an effect that approximately similar to the effects of pre-operative dopaminergic therapy[6, 7]. Some authors have found that STN-DBS treatment alone improved postural sway, whereas dopaminergic treatment increased postural sway abnormalities[8, 9]. In contrast to these studies, a study has found that postural stability worsened after STN stimulation, but not after GPi stimulation[10].

Also, it is still controversial whether the addition of STN stimulation to levodopa provided additional benefit to postural instability and gait impairments. Some authors have suggested that the combined therapy may cause a synergistic effect on the gait and balance function[8, 9, 11], whereas some authors have reported that the combined therapy had no additional positive effects on gait and balance parameters[12–14]. Consequently, data on this issue is limited and remains obscure. In this study, we aimed to evaluate the efficacy of combined therapy of bilateral STN stimulation and dopaminergic medication on balance and mobility in patients with PD.

Materials and methods

This cross-sectional study was approved by the University of Akdeniz Ethics Committee. Written informed consents were given by all participants in line with Declaration of Helsinki. In the present study, eighteen PD patients, who had been implanted with bilateral STN stimulation systems (Lead model 3387 and 3389, Medtronic, Minneapolis, USA) at Akdeniz University, were enrolled. All surgeries were performed by the same neuro-

surgeon (T.U). Before surgery, contrast-enhanced T1 and T2-weighted Magnetic resonance images (MRI) were taken. On the day of the operation, the Leksell stereotactic G frames (Elekta Instrument AB, Stockholm) were placed on the patients' heads under local anesthesia. The patients' non-contrast brain tomographies (CT), with a slice thickness of 1 mm, were taken and CT images were transferred to the planning software and fused with MRI images. These images were coordinated to the system of the Leksell G frame (Elekta Instrument AB, Stockholm). Microelectrode recording (MER) (Lead point, Medtronic Minneapolis) and macro stimulation on the target selected with MER were performed to confirm the target during surgery. A DBS electrode (Lead model 3387 and 3389, Medtronic, Minneapolis, USA) was implanted in the location, which was considered as the correct target. The positionings of electrodes on post-operative CT scans were compared with preoperative MRI. DBS programming was initiated approximately one week after surgery. The optimal setting was defined as the one with maximum reduction in motor symptoms without adverse effects. Also, only participants with at least six months of bilateral STN stimulation were included in this study to ensure that DBS settings and dopaminergic treatment were optimized. Participants met the following inclusion criteria: (1) diagnosis of idiopathic PD according to standard criteria; (2) at least six months bilateral STN stimulation treatment; (3) able to walk ten meters without an assistive device in medical ON condition treatment. Patients with a history of dementia (i.e., Mini-Mental Status Exam/MMSE score 24<30), who had serious comorbid diseases or other neurological diseases, and who were using medication that could impair balance and gait, were excluded. The data, including the patients' age, disease duration, age at DBS surgery, the period between the surgery and participation in the study, were collected. The patients' medications for PD were evaluated using levodopa-equivalent daily dose (LEDD).

A modified Hoehn and Yahr staging[15] and the *Unified Parkinson's Disease Rating Scale (UPDRS)*[16] were applied to assess the patients' clinical characteristics. The UPDRS has four parts: Part I concerns "non-motor experiences of daily living", Part II concerns „motor experiences of daily living, "Part III is related to the „motor examination", and Part IV concerns „motor complications. The UPDRS part-III postural instability/gait disorder (PIGD) scores (sum of items 3.9-3.13) and the UPDRS part III postural stability item (item 3.12) were calculated separately. First of all, the patients were evaluated one hour after taking the usual dose of levodopa (L-dopa) (mean 113 mg) in stimulation ON condition. Then the stimulation was turned off and the patients were retested at least 45 minutes after stimulation was switched off[17]. The UPDRS part III, mobility and balance tests including the Berg Balance Scale, the Mini-Balance Evaluation Systems Test (Mini-BESTest), the Timed "Up and Go" (TUG) test, dual-task TUG test, and Forward Functional Reach (FFR) Test were applied under two conditions; Stim-ON/Med-ON and Stim-OFF/Med-ON.

The Berg Balance Scale (BBS) is an objective measure of balance abilities and consists of 14 simple tasks, related to balance, ranging from sitting position to standing up to standing on one foot. All items are scored from zero to four and the maximum total score is 56 points. A higher score indicates better performance[18, 19].

Mini-Balance Evaluation Systems Test (Mini-BESTest) is a clinical assessment of balance. The *Mini-BESTest* is highly reliable in people with PD[20]. The *Mini-BESTest* has a total possible score of 28 points from 14 items that are each scored from 0-2, with higher scores indicating better balance. The Mini-BESTest includes four subsections corresponding to anticipatory, reactive postural control, sensory orientation, and dynamic gait components of balance[21].

The Timed Up and Go (TUG) Test evaluates the time of a sequence of locomotor tasks, consisting of getting up from a chair, walking three meters, turning around, returning to the chair, and sitting comfortably in the same chair. The average time required to complete the TUG test has been reported[22]. The *Dual task TUG (DT-TUG) test* was assessed with a cognitive task, counting backward by sevens from 100 (TUG-cognitive).

The Forward Functional Reach (FFR) Test is a reliable, valid, clinical measure of dynamic balance. The participant is asked to elevate his/her dominant arm to shoulder height and then to perform a maximum forward reach as far as possible without moving his/her feet and losing balance[23].

Statistic

The Windows-based SPSS 23 (Statistical Package for the Social Sciences) analysis program was used for statistical analysis. The normal distribution of the data was examined using the Shapiro-Wilk Test. The Wilcoxon test was used for intragroup comparison of ordinal variables or abnormally distributed non-parametric data sets. A p-value of less than 0.05 was considered to show statistically significant result.

Results

A total of 18 idiopathic PD patients, 8 of whom were women were enrolled. Mean age was 59.5±9.1 (range: 41-71) years. The mean age at the time of surgery was 56.3±9.5 (range: 38-69) years. The patients were diagnosed with PD at the mean age of 44.5±9.5 (range: 25-59) years and they underwent DBS surgery after a mean time period of 11.8±6.2 (range: 5-28) years following PD diagnosis. The mean duration time of bilateral STN

stimulation therapy was 19.5±18.3 (range: 6-67) months. **Table 1** shows clinical characteristics, LEDD, stimulation settings, and UPDRS score of the patients.

Table 2 summarizes the mean of total Mini-BESTest scores and Mini-BESTest subscores, total Berg Balance scale, FFR score, the TUG test, the DT-TUG test, and PIGD subscore and postural instability item of the UPDRS part III with standard deviations in the Stim-OFF/Med-ON and Stim-ON/Med-ON conditions. The UPDRS part III total score and PIGD subscore significantly improved after stimulation was turned on (p=0.001), but the postural instability item of the UPDRS part-III did not change significantly (p=0.1). There were no significant differences between Stim-OFF/Med-ON and Stim-ON/Med-ON conditions for total Mini-BESTest scores, total Berg Balance Scale score, FFR score (p>0.05 for all of them). The mean score of dynamic gait components of balance in the Mini-BESTest was better in Stim-ON/Med-ON condition compared to Stim-OFF/Med-ON condition (p=0.02). The TUG test was significantly improved in Stim-ON/Med-ON condition compared to Stim-OFF/Med-ON condition (p=0.03). DT-TUG test did not significantly change when Stimulation ON or OFF in Med-ON condition (p=0.1).

Table 1. *Clinical characteristics of patients*

	Mean ± SD
Duration of disease (years)	13.3±6.7
Duration of DBS treatment (months)	19.5±18.3
Total levodopa equivalent daily dose/total LEDD (mg)	113.5±25
UPDRS part I score	9.2±6.3
UPDRS part II score	14.2±9.1
UPDRS part IV score	4.3±4.5
Hoehn-Yahn staging Med-ON/Stim-ON	2.4±0.2 (2.3)
DBS voltage (left mean/right mean ± left SD/ right SD)	2.4/2.03±0.6/0.4
DBS pulse width (μs) (left mean/right mean ± left SD/right SD)	86.6/85±14.1/15.4
DBS frequency (Hz) (left mean/right mean ± left SD/right SD)	125/125±7.8/7.8

SD: standart deviation, UPDRS: The Unified Parkinson's Disease Rating Scale, Med-OFF/Stim-ON: Medication-OFF/Stimulation-ON, Med-ON/Stim-ON: Medication-ON/Stimulation-ON, Med-ON/Stim-OFF: Medication-ON/ Stimulation-OFF, μs: microsecond, Hz: Hertz

Discussion

The present study evaluated the effect of the combination therapy of dopaminergic medication and bilateral STN stimulation on balance and mobility in PD. This study showed that the addition of STN-DBS to dopaminergic treatment had a synergistic effect on motor symptoms and some mobility performance, but not on postural stability and dual-task mobility.

Dopaminergic treatment can improve some balance systems, such as anticipatory postural adjustments in preparation for voluntary movements, and dynamic balance during movements, whereas it can worsen or not change some balance systems, such as balance during quiet stance, and reactive postural adjustments to external perturbations. Also, the response to dopaminergic treatment in postural control may depend on the stage of the disease[2]. In the literature, the different results on the effect of STN-DBS treatment alone and combined therapy of bilateral STN-DBS and dopaminergic medication on postural control have been reported. Some studies, evaluating the effect of STN-DBS alone on postural control, have reported that STN-DBS increased balance parameters[24, 25]. Another study has shown that balance was better in treated cases (Med-ON/Stim-ON) compared to untreated cases (Med-OFF/ stim-OFF) in PD patients. However, this study could not determine the effects of either medication alone or stimulation alone on balance[26]. Our study found that combined therapy had an additional effect on only dynamic gait component of the balance parameter, but not on anticipatory, reactive postural control, sensory orientation systems of other balance parameters. The total scores for Berg Balance Scale, Mini-BESTest, and FFR did not change when stimulation was turned on under Med-ON condition. *McNeely*, et al., have also reported that both STN-DBS therapy alone and dopaminergic therapy alone improved balance parameters (Mini-BESTest), but the combination therapy did not provide a significant additional benefit on balance[13]. Another study has also showed that the posturography measures during unperturbed stance and externally perturbed stance under L-dopa treatment were similar to those under STN-DBS treatment in PD patients, and some abnormal tilt reactions of the patients were resistant to L-dopa alone, STN stimulation alone, and combined treatment[14]. Our findings are consistent with these studies[13, 14] and demonstrated that STN-DBS had a similar effect to dopaminergic medication on postural control. On the other hand, some authors have concluded that STN-DBS had an improvement effect on both the dopaminergic and non-dopaminergic pathways of postural control[8, 9, 27]. *Dehail*, et al., reported that dopaminergic treatment alone worsened

Table 2. *Results of balance, gait, and UPDRS part III assessments of the patients*

	Stim-OFF/Med-ON Mean ± SD	Stim-ON/ Med-ON Mean ± SD	p
Total UPDRS part-III score	49.8±11	27.8±12	*0.001***
PIGD subsection score	6±4.3	3.4±2.5	*0.001***
UPDRS part-III postural instability item score	0.9±1.2	0.5±0.9	0.1
Mini-BESTest score	18.5±7.2	20.5±4	0.2
Anticipatory score	4.1±1.6	4.3±1	1.0
Reactive postural control score	2.6±1.8	3.1±1.1	0.1
Dynamic gait components of balance score	6.2±3	7.3±2.3	*0.02**
Sensory orientation score	5.3±2	5.6±1.4	0.3
BBS score	47.8±14	51.9±4.9	0.2
TUG test (sn)	11.3±8.3	10.7±5.4	*0.03**
DT-TUG test (sn)	17.5±14.5	18.1±13.3	0.2
FFR (cm)	20.8±10	22.6±8.2	0.9

Med-ON/Stim-OFF: Medication-ON/Stimulation-OFF, Med-ON/Stim-ON: Medication-ON/Stimulation-ON, SD: Standart deviation, UPDRS: The Unified Parkinson's Disease Rating Scale, PIGD: Postural instability/gait disorder, Mini-BESTest: Mini-Balance Evaluation Systems Test, BBS: Berg Balance Scale, TUG: Timed Up and Go, DT-TUG: Dual-Task Timed Up and Go, FFR: Forward Functional Reach, cm: centimeter
*P-values obtained from Wilcoxon test.
*P < 0.05, **P < 0.01.

the postural sway area, but combination therapy of STN-DBS and medication reduced postural sway area and displacement[27]. Similarly, other studies demonstrated that the combined therapy improved postural sway compared to medication alone, since STN-DBS reversed the negative effects of levodopa on the postural sway[8, 9]. Also, *Gauchard*, et al., have shown that combined treatment improved postural control by increasing motor abilities and specific postural related mechanisms[28]. In contrast to these studies, a study has reported that reactive postural adjustments in Med-ON/Stim-ON condition 6 months after surgery, were worse than Med-ON condition before surgery for patients, who had undergone STN-DBS treatment; whereas reactive postural adjustment had not worsened in patients under GPI-DBS treatment. They concluded that this worsening of postural control after STN surgery was due to exacerbation of bradykinetic postural responses[10].

This study found that a combination of bilateral STN-DBS and levodopa provided an additional improvement in gait performance assessed by the PIGD subsection score of the UPDRS part III and TUG test. Similar to our findings, some studies have also reported that STN DBS alone and dopaminergic medication alone had similar positive effects on spatiotemporal gait parameters and combined therapy led to a synergistic positive effect[11, 29–31]. On the other hand, some authors have reported that combination of dopaminergic medication and STN-DBS therapy had no synergistic effect on gait parameters[12, 13, 32]. Also, other gait features, such as dual-task gait impairments, improved with dopaminergic medication alone, as well as with bilateral STN DBS alone; however, no additional improvement with combined therapy has been reported[13]. This study also showed that dual-task mobility did not respond to combined therapy. Dual-task gait impairments in Parkinson's disease are associated with reduced spatial focusing of cortico-striatal activity. This pattern of striatal activity may be explained by a loss of segregation between different cortico-striatal loops within the striatum due to dopaminergic mechanisms[33]. Additionally, dysfunction in non-dopaminergic physiological mechanisms, such as the noradrenergic system, the glutamatergic system, and the cholinergic system, might have contributed to gait and balance impairments and cognitive disorders in PD[1]. We concluded that the lack of synergistic effect of combined therapy on both dual-task walking and postural instability was linked to these non-dopaminergic pathways in PD.

This study had several limitations. An important limitation was the small number of patients. Another important limitation was our inability to determine the effect of STN-DBS therapy alone or levodopa on balance and mobility in PD patients. Also, in our clinic center, optimum stimulation programming is adjusted according to

the patients' improvement of motor symptoms, including tremor, rigidity, bradykinesia, and axial symptoms, such as speech, gait function, and postural control stimulation. The stimulation settings and localization of active contact may worsen or improve both balance and gait performance. Our results of the response to combined therapy on balance might have been affected by this optimal DBS setting. Consequently, we saw that optimal stimulation setting improved motor symptoms significantly, which led to increased mobility without worsening axial symptoms.

In conclusion, both dopaminergic and non-dopaminergic pathophysiological mechanisms are involved in balance and gait disorders. The combination therapy may have a synergistic effect on motor symptoms and some gait parameters with a similar dopaminergic effect, but not on postural stability and dual-task walking. However, the acute and long-term effects of bilateral STN-DBS treatment on axial symptoms are still controversial. Further research is needed to explore the acute and long-term effects of STN-DBS on the dopaminergic and non-dopaminergic pathways for axial symptoms.

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