Original Article

Functional Outcome of Bilateral Subthalamic Nucleus-Deep Brain Stimulation in Advanced Parkinson's Disease Patients: A Prospective Study

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Abstract

Background: Deep brain stimulation (DBS) is an accepted modality of treatment in patients with Parkinson's disease (PD). Although DBS was approved in advanced PD, it is being done in early PD as well. It was mainly developed to help the patients of PD to overcome the adverse motor effects associated with treatment and treatment failure. **Objective:** The objective is to study the efficacy of subthalamic nucleus (STN)-DBS procedure in patients with PD. **Materials and Methods:** This was a prospective, single-center, follow-up observational study using a direct, structured interview of 40 selected PD patients. Preoperative assessment using Unified PD Rating Scale-III (UPDRS-III), Montreal Cognitive Assessment (MOCA), and Parkinson's Disease Questionnaire-39 were done. All the patients underwent DBS. Postoperatively, similar assessment was done during follow-up period of 6 months. The results were analyzed using Student's *t*-test. **Results:** The total score of UPDRS-III was reduced by 35% after STN-DBS intervention which was statistically significant ($P < 0.05$). STN-DBS intervention was successful in significantly reducing all UPDRS-III subscores but failed to reduce the scores in case of postural stability. MOCA scores of the patients were not found to be affected by STN-DBS intervention ($P = 0.1466$). Similar findings were also observed for MOCA subscores, but there was significant improvement of verbal fluency in all patients. Quality of life(QoL) improved significantly in all patients after STN-DBS intervention in all areas. Lower baseline UPDRS-III scores were found to enhance the QoL both in "off" and "on" state. However, prolonged disease duration and older age at PD onset were found to be hampering factors in the improvement of QoL. **Conclusions:** STN-DBS is a safe procedure and can be performed in all patients of PD who develop disabling motor fluctuations to improve their QoL irrespective early or advanced disease.

Keywords: Dyskinesia, Parkinson's disease, quality of life, subthalamic nucleus-deep brain stimulation

Introduction

In Parkinson's disease (PD), there is a gradual depletion of neurotransmission by dopamine. The disease is characterized mainly by motor symptoms such as postural instability, rigidity, rest tremors, and bradykinesia. Patients eventually become dependent on family and hence place a burden on the caregivers, as well as society.[1] Long-term levodopa use is associated with various adverse effects such as motor fluctuations and dyskinesia.[2]

Deep brain stimulation (DBS) has been shown to be efficacious in overcoming the issues associated with failure of therapy and drug-induced motor complications.[3] Over the period of time, its acceptance has increased as it proved to be effective in addressing these patient-related issues and also has been found to improve the quality of life (QoL).[4] Subthalamic nucleus (STN) and globus pallidus interna (GPi) are the well-proved targets for DBS in PD patients. Ventralis intermedius and zona incerta are also being tried as targets in tremor-predominant PD patients. Pedunculopontine nucleus stimulation is being tried for freezing of gait.[5]

Randomized controlled trials have shown that DBS is superior to best medical therapy.[6-9]

In a recent meta-analysis of four randomized controlled trials comparing STN versus GPi-DBS, Wang *et al*. found that compared with GPi, DBS, and STN-DBS was associated with decline in selected cognitive domains including attention, working memory and processing speed, phonemic fluency, learning and memory, and global cognition. However, there were no significant differences in terms of QoL or psychiatric effects, such as depression and anxiety, between the two groups.[10]

Perestelo-Pérez *et al*. in their meta-analysis of various RCTs concluded that DBS is efficacious in "control of motor signs and improvement of patients' functionality and QoL and

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DOI: 10.4103/aian.AIAN_357_18

more controlled research is required on the neurocognitive and psychiatric effects of DBS."[11] However, the best target for DBS is still controversial with patient selection and lead location being important predictors of response. DBS in PD patients with early motor complications has also shown to be effective in controlling motor symptoms and improving QoL when compared to best medical therapy.[12]

The exact mechanism of action of STN-DBS remains unclear even after 20 years of experience. Changes in the motor cortical activity due alteration in antidromic signals traveling from STN after high-frequency DBS has been proposed as one of the mechanisms of action.[13]

As there are few studies reported from India, we undertook this single-center, prospective study, to know the effects of bilateral STN-DBS on motor control, cognition, and on QoL of advanced PD patients who underwent DBS surgery.

Materials and Methods

This was a prospective, single-center, follow-up observational study using a direct, structured interview of 40 selected PD patients carried out at Nizam's Institute of Medical Sciences, Hyderabad, from June 2015 to December 2016.

Inclusion criteria

1. All idiopathic PD patients who were found eligible as per the CAPSIT-PD protocol and were willing to undergo STN-DBS surgery at Nizam's Institute of Medical Sciences
2. PD disease duration of ≥5 years, moderate disease (Unified PD Rating Scale-III [UPDRS-III] score of ≥30 in "off" state), good response to levodopa (improvement in UPDRS Part-III by ≥30%), and normal cognition (Montreal Cognitive Assessment [MOCA] >25).

Exclusion criteria

1. Patients with secondary PD, Parkinsonism plus syndromes.
2. Patients who had not given consent.

The study was approved by the institutional ethics committee. All patients were informed of the aim of the study and all patients provided written informed consent.

All demographic and clinical data were collected. During preoperative assessment, current medications and their doses were recorded.

Modified Hoehn and Yahr staging in "off," and UPDRS-III in medication "on" and "off" state was performed in all patients.

Cognitive assessment using MOCA score was performed in "on" state. All patients were interviewed for QoL using Parkinson's Disease Questionnaire (PDQ-39) questionnaire in the "on" state. The key relative was also interviewed for corroborating the details given by the patient. The differences and inconsistencies in the versions and doubts of both patients and family were addressed and consistency achieved.

All patients were operated by a qualified neurosurgeon. Stereotactic surgery was performed using CRW frame under MRI guidance with intraoperative 5-channel microelectrode recording. Final lead placement in bilateral subthalamic nuclei was based on intraoperative stimulation. Postoperative MRI was performed and stimulation was based on that.

All patients were managed postoperatively on a combination of dopamine replacement therapy as well as DBS. All patients had monopolar stimulation with frequency of 130 Hz, pulse width of 60 μs, and amplitude ranged from 2.5 to 4.0V based on requirement.

Follow-up after deep brain stimulation

Forty patients underwent DBS and were followed up after a period of 6 months and were again assessed. The following were recorded: medication usage, UPDRS-III in stimulation "on" medication "off" and stimulation "on" medication "on" states, PDQ-39, and MOCA scores.

The preoperative and postoperative characteristics were compared.

Statistical analysis

Continuous variables were presented as mean ± 2 standard deviation. Student's *t*-test and Wilcoxon ranked-sum test were used to study the differences between means. All tests were two tailed and $P < 0.05$ was considered statistically significant.

Results

Table 1 shows clinical characteristics of the study participants. The duration of PD ranged from 4 years to 18 years with a mean of 7.32 years. The minimum age at onset of PD was 22 years and the maximum was 64 years, thus showing that PD cases occur in young to old age. The mean age at surgery was 55.5 years with a range of 32 years to 74 years.

Table 2 shows the effect of DBS on UPDRS-III score and the subscores. In the off-medication conditions, compared with preoperative off scores, STN stimulation reduced the total UPDRS-III motor score by 35% ($P < 0.0001$) at a minimum of 6-month follow-up period. This improvement was observed for all the UPDRS-III subscores except for postural stability. In the on-medication conditions, compared with preoperative on scores, STN stimulation reduced the total UPDRS motor score by 23% ($P < 0.0001$) at a minimum duration of 6-month follow-up period. This improvement was observed for UPDRS-III subscores of tremor (improvement; 18%, $P < 0.0371$), rigidity (improvement; 32%, $P = 0.0001$), and for bradykinesia (improvement; 17%, $P = 0.0015$). There was no statistically significant improvement noted in UPDRS-III subscores for speech (improvement; 11%, $P = 0.5703$), gait (improvement; 12%, $P = 0.4211$), and for postural instability (improvement; 19%, $P = 0.1599$).

Table 3 shows the effect of DBS on MOCA score. There was no significant difference in the total MOCA scores before

and after STN stimulation (28.6 vs. 28.4, $P = 0.1466$). In the MOCA subscores, there was reduction only in the verbal fluency as compared to preoperatively, which was statistically significant (0.97 vs. 0.72, $P = 0.0009$).

Table 4 shows the effect of DBS on PDQ-39 scores and subscores. DBS was found to be very effective in improving the QoL in all areas of QoL using PDQ-39 scores. Total score reduced significantly from 39 to 19.8. All subscores also reduced significantly after DBS except social support where there was no significant reduction ($P > 0.05$).

Table 5 shows factors predicting improvement and nonimprovement in PDQ-39 scores. The factors that improved the PDQ-39 score were lower baseline UPDRS-III scores both in "off" and "on" state. On the other hand, factors resulting in reduced improvement were older age at PD-onset and longer duration of disease.

Discussion

PD is a chronic neurodegenerative disease which causes significant morbidity and loss of functional capacity. The treatment options include a variety of drugs including levodopa, dopamine agonists, MAO-B and COMT inhibitors, anticholinergics, and the search is on for disease-modifying therapies. In a landmark-randomized study comparing best medical therapy versus DBS in patients with advanced PD, bilateral STN-DBS has been found to be superior to best medical treatment with a gain of a mean of 4.6 h/day on times without troublesome dyskinesia. About 71% of patients on DBS had meaningful improvement with an improvement in QoL scores after DBS.[7,14] Since then, studies have shown a consistent effect of STN-DBS which persists even after 10 years after stimulation of choice in patients with PD.[15,16] The present study also gives similar results.

In the present study, the overall UPDRS-III scores improved significantly after STN-DBS intervention. The improvement was also noted in all the subscores of UPDRS-III in medication-off status. In the on state also, the UPDRS-III score improved by 23%. Other studies also showed similar results.[17-19]

The subscores such as postural instability, gait, and speech did not improve in the on state even after STN-DBS. Few previous studies reported a gradual deterioration in the axial symptoms in the on state after STN-DBS. Postural instability and gait problems do not respond to dopaminergic therapy. This may be partially explained by the fact that there is dysfunction of nondopaminergic circuits (serotonergic, noradrenergic, and cholinergic) in PD. STN-DBS is shown to be useful only in "dopamine-mediated motor symptoms" that respond to levodopa and consequently does not relieve axial symptoms. Resistance of existing axial symptoms and appearance of new gait problems reflects the progression of the disease.[19]

Table 1: Clinical characteristics of the study participants ($n=40$)

Characteristics	Range	Mean±2SD
Duration of PD (years)	4-18	7.32±2.78
Age at onset of PD (years)	22-64	47.7±10.1
Age at surgery (years)	32-74	55.5±9.73

SD=Standard deviation, PD=Parkinson's disease

Table 2: Effect of deep brain stimulation on Unified Parkinson's Disease Rating Scale-III score and the subscores

Scores	On/off state	Pre-DBS	Post-DBS	*P*
UPDRS-III motor score total	Med off	61.05±10.8	39.6±10	<0.0001
	Med on	16.3±5.8	12.47±6.1	<0.0001
Tremor (item 20-21)	Med off	12.9±5.5	8.32±3.2	<0.0001
	Med on	2.20±1.8	1.8±2	0.0371
Rigidity (item 22)	Med off	14.52±3.9	9.2±2.4	<0.0001
	Med on	4.3±5.4	2.92±2.2	<0.0001
Bradykinesia (item 23-26)	Med off	24.7±5.4	17.05±5.03	<0.0001
	Med on	7.52±3.2	6.27±3.01	0.0015
Speech (item 18)	Med off	1.55±0.8	1.15±0.06	<0.0001
	Med on	0.22±0.4	0.20±0.4	0.5703
Gait (item 29)	Med off	1.77±0.9	1.35±0.6	<0.0001
	Med on	0.42±0.7	0.37±0.6	0.4211
Postural stability (item 30)	Med off	1.77±0.8	1.42±0.6	0.0030
	Med on	0.52±0.6	0.42±0.6	0.1599

DBS=Deep brain stimulation, UPDRS=Unified Parkinson's Disease Rating Scale

Table 3: Effect of deep brain stimulation on Montreal Cognitive Assessment Score

MOCA score	Pre-DBS	Post-DBS	*P*
MOCA score total	28.6±1.8	28.4±2.1	0.1466
Visuospatial	4.07±1.4	4.12±1.5	0.1599
Attention	5.90±0.3	5.90±0.3	1.0000
Verbal fluency	0.97±0.1	0.72±0.4	0.0009
Abstract thinking	1.92±0.2	1.95±0.5	1.000
Memory recall	4.65±0.5	4.65±0.5	1.000
Orientation	5.97±0.1	5.92±0.2	0.3235

MOCA=Montreal Cognitive Assessment Score, DBS=Deep brain stimulation

Table 4: Effect of deep brain stimulation on Parkinson's Disease Questionnaire-39 scores and subscores

PDQ-39 score	Pre-DBS	Post-DBS	*P*
Total score	39.0±19.7	19.8±11.9	<0.0001
Mobility	14.8±8.0	7.67±5.6	<0.0001
Activities of daily living	6.70±5.1	3.62±3.0	<0.0001
Emotional well-being	6.07±3.6	3.05±1.6	<0.0001
Stigma	3.02±2.9	1.92±1.8	0.0012
Social support	0.30±0.9	0.20±0.6	0.2099
Cognition	3.25±2.5	1.42±1.6	<0.0001
Communication	1.10±1.8	0.80±1.3	0.0005
Bodily support	3.05±2.0	1.82±0.8	<0.0001

DBS=Deep brain stimulation, PDQ=Parkinson's Disease Questionnaire

Table 5: Factors predicting improvement and nonimprovement in Parkinson's Disease Questionnaire-39 scores

Factors predicting improvement in PDQ-39 scores	Pearson correlation coefficient	*P*
Age	0.25	0.2499
Age at PD onset	0.21	0.336
Duration of PD	0.09	0.964
UPDRS-III		
Off state	0.57	0.0004
On state	0.41	0.050
MOCA score	0.04	0.86
Factors predicting nonimprovement in PDQ-39 scores		
Age	0.31	0.225
Age at PD onset	0.478	0.050
Duration of PD	0.612	0.009
UPDRS-III		
Off state	0.37	0.14
On state	0.33	0.20
MOCA score	0.409	0.103

UPDRS=Unified Parkinson's Disease Rating Scale, PDQ=Parkinson's Disease Questionnaire, MOCA=Montreal Cognitive Assessment Score, PD=Parkinson's disease

Kleiner-Fisman *et al*. noted that STN-DBS was effective in improving the activities of daily life in advanced cases and it also improves the motor activity.[20] St George *et al*. observed that STN-DBS may be useful and helpful, especially in patients with postural and gait disability.[21] Perestelo-Pérez *et al.* in their review of six studies found that DBS with medication was more effective than drugs alone.[17]

In our study, we assessed cognition using MOCA scale preoperatively and after minimum of 6 months following STN stimulation. The total MOCA score and MOCA subscores did not show any significant decline postoperatively except for verbal fluency.

In a qualitative review of initial studies on neuropsychological sequel of STN-DBS, Woods *et al.* concluded that the most consistently reported findings were reduction in verbal fluency and improvement in self-reported symptom of depression. They noted that 30%–50% of the patients had consistent improvement even at the end of 3 years of follow-up. Reports of changes in global cognitive functioning, memory, attention, and executive function are less common and severe cognitive impairments are seen in <1%–2% of the patients.[22] Some aspects of cognition improve with STN-DBS. Halpern *et al*. noted improvement in vasomotor sequencing, psychomotor speed, and working memory.[23]

In our study, there was a significant improvement in QoL following STN-DBS using PDQ-39. There was an improvement of 49% after STN stimulation which was consistent with other studies.[22,24] Except for social support, all the rest of subscores of PDQ-39 showed a significant improvement in the present study. Okun *et al*. carried out sample size weighted analysis which also showed the improvement in QoL with a summary index of 34.5% ± 15.3%. The author found that dimensions of QoL such as mobility, stigma, and emotional well-being improved, whereas dimensions like social support showed modest benefit.[25] The effect of DBS on late stages of PD in the improvement of QoL needs to be reviewed.

Limitations

1. We did not assess the exact location of the electrode within the STN as that may also probably contribute to the changes in the parameters
2. We assessed all the scores at 6 months following STN stimulation. However, in some patients, optimal setting of the neuromodulator may take 9–12 months and hence the benefit may be more evident at that time. As this is an unblended study, the placebo effect due to dopamine release from the striatum in anticipation of the improvement may still persist at 6 months thus falsely magnifying the benefit
3. A total of 40 patients were studied. The studies using large number of patients may give a better assessment of outcome.

Conclusions

DBS targeting the bilateral STN showed significant improvement in UPDRS-III motor scores, both in medication-off and medication-on states. The improvement was noted for most of the subscores in medication-off state than in medication-on state. There was significant improvement seen in QoL as assessed by PDQ-39 score. The total PDQ-39 and most of the subscores showed significant improvement. Longer duration of disease and early age of onset of PD resulted in reduced improvement in QoL after STN-DBS. There was no significant decline in cognition as assessed by MOCA score except for verbal fluency. These results reinforce that STN-DBS is a safe procedure and can be performed in all patients who are having medically refractory PD and having severe drug-induced dyskinesia for improving their QoL.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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