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EARLY OUTCOME OF SUBTHALAMIC NUCLEUS - DEEP BRAIN STIMULATION (STN-DBS) IN THE ADVANCED STAGE OF PARKINSON DISEASE - A TRIAL OF IRANIAN PATIENTS

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ABSTRACT

Introduction: To improve the debilitating features of Parkinson disease (PD) various medical and surgical approaches are available. Subthalamic nucleus deep brain stimulation (STN-DBS) was appeared to be a promising method during last two decades. This study aimed to evaluate early motor outcomes of this procedure in one of the first trials of Iranian patients. **Materials and Methods:** Thirty-seven patients with advanced Parkinson disease, unresponsive to common medical agents, underwent bilateral STN-DBS. For assessment of motor function parameters "Unified Parkinson Disease Rating Scale III" (UPDRS III) was used. We compared total scores and sub-scores in three categories performed as 1) preoperative off-medication, 2) preoperative on-medication and 3) six months postoperative on medication. Reduction in drug consumption was assessed considering administered doses of l-dopa before and after surgery in stable states. **Results:** Twenty six males and 10 females with mean age of 50 years were evaluated (one patient expired before 6-month follow-up). Mean total scores of UPDRSIII were 5.2±54.52, 2.88±18.22 and 3±12.8 in the three categories, respectively ($p=0.003$). PostHoc analyses showed significant improvement among all categories. Analysis of sub-scores also revealed significant amelioration in rigidity, action tremor, hand movement, leg agility, finger tap and rapid alternating movement in on-medication phases of pre- and post-operation (all with $p<0.01$). Mean dosage administered of l-dopa were224±1296 mg/d and 174±782 mg/d before and after surgery, significant decline was observed. ($p<0.001$). **Conclusion:** Our results indicated that bitemporal STN-DBS can result in significant short-term improvement of the motor symptoms especially in debilitating symptoms such as rigidity and tremor in advanced PD. It also accompanies with remarkable reduction in the needed doses of drugs. The findings support other studies with similar follow-up interval; however, continuous evaluations are needed for long-lasting results.

INTRODUCTION

To improve the debilitating features of Parkinson disease (PD), surgery was the main frame for the patients suffering from the disease in the early 19th century.[1] Lesions of the thalamus and pallidum leads to debilitating tremor and rigidity.[2,3] With the advent of oral Levodopa therapy, a drastic reduction in the number of surgeries performed on PD patients with additional advantage of improving akinesia, was observed. However, after a few years complications of chronic levodopa intake, mainly dyskinesias and on-off fluctuations, started to raise other challenges.[4,5]

This led to resuming surgical approaches such as ablation of globus pallidus. Pallidotomies seemed to have a good effect on contralateral tremor, rigidity, and dyskinesias[6-9] but it is accompanied with high rates of permanent adverse effects.[10-12] This prompted clinicians to search for a better target. There has been a rising interest in STN as a new target considering its inhibitory function within the basal ganglia loops.

Development of high frequency deep brain stimulation (DBS) in neurosurgery provided a better alternative for physicians to alleviate movement disorder.[13,14] This procedure was performed on different nuclei.[15,16] In

1993, Benabid performed Subthalamic nucleus deep brain stimulation (STN-DBS) in a patient with advanced PD.[17] Subsequently many centers followed and now the procedure is widely accepted as a treatment for patients unresponsive to medical agents. Comparing to previous procedures it is reversible, less invasive and can be performed bilaterally.[19-23]

However, short and long term follow-up data are needed to evaluate the efficacy and complications of STN-DBS. Our centre was the first one in Iran which applied the procedure for advanced Parkinson disease. Here we will report 6-month follow-up of patients regarding their motor function and drug administration.

MATERIAL AND METHODS

Sample
Thirty seven patients with severe Parkinson disease were enrolled between 2004 and 2007. They were referred to Rasoul Akram Hospital affiliated to Iran University of Medical Sciences (IUMS), where STN-DBS procedure for treatment of PD performed in Iran.

Individuals were included in case of having >30% improvement in levodopa challenge test. We excluded patients with significant psychiatric or behavioural illness, any focal brain abnormalities on MRI, severe medical problems and general contraindications for surgery such as severe hypertension or coagulopathy. The study was approved by our Institutional Review Board and written informed consents were provided by all subjects.

Surgery
Streotactic MRI imaging was applied to provide direct visualisation of subthalamic nucleus. Tetrapolar electrodes were used simultaneously or subsequently for electrophysiological exploration. The process was performed under local anesthesia and a trained neurologist assessed clinical response to DBS in the operating room. After ascertaining the optimal track, the corresponding microelectrode was replaced by a chronic lead. We placed subcutaneous pulse generator after several days under general anesthesia. During the next week programming was done by the neurologist.

Clinical evaluation
Motor performance was evaluated using UPDRS part III including items for speech, facial expression, resting tremor, action tremor, rigidity, finger tap, hand movement, rapid alternating movement, leg agility, arising from chair, gait, bradykinesia and posture stability each with a score between 0 to 4. Lower scores reflect better performances. Preoperative UPDRSIII assessments were conducted in the on- and off-medication state. Postoperative scores were evaluated only in the stimulator-on condition with medication at 6 months of follow-up, because all patients kept their stimulators on and using medication continuously.

Medication
A stable level of l-dopa maintained for at least 2 months prior to surgery was considered as preoperative medication. For postoperative measurement, the administered dose of the drug at 6 months after surgery was taken into account. No one in our study had off-medication state after surgery.

Statistical analysis
Descriptive analysis of the data is presented as means and standard deviations. UPDRS III total score and items' sub-scores in two pre-operative and 6 - month follow-up measurements were compared using repeated-measure ANOVA. For analysing dichotomous evaluations, like drug doses before and after surgery paired t-test was applied. A p-value <0.05 is considered to be statistically significant. All data have been analyzed by SPSS version 15.

RESULTS

Thirty seven patients with advanced Parkinson disease underwent STN-DBS surgery. One of them died of myocardial infarction before discharge. Rests of the patients were included in the study to evaluate 6-month follow-up. Mean age of patients was 50 ± 3 ranging from 32 to 72 years. The mean duration from beginning of the symptoms till the time of the surgery was 11.28 ± 1.88 years. Bilateral approach of STN DBS was applied for all patients.

Pre-operative UPDRS III scores of off- and on-medication measurements were 54.52 ± 5.4 and 18.22 ± 2.88, respectively. Postoperative score yielded 12.8 ± 3.14 that showed significant difference comparing with both preoperative scores ($p<0.001$). Analysis of UPDRS III sub-scores in two preoperative measurements revealed significant improvement in all items after l-dopa consumption ($p<0.05$). Comparison of findings from two on-medication phases revealed performing DBS led to significant alleviation in rigidity, action tremor, finger tap, rapid alternating hand movement and body bradykinesia (Table 1).

Complication
Neurostimulation parameters of lead coordinates are available in another report of technical issues of the

TABLE 1. Scores and sub-scores of UPDRS III in three measurements of preoperative off-medication, preoperative on-medication and six months postoperative on medication.

	Preoperation off-medication	Preoperation on-medicaion	Postoperation on-medication	P value*
UPDRSIII (total)	54.52±5.4	18.22±2.88	12.8±3.14	0.000
Speech	1.94±0.28	1.11±0.24	1.05±0.28	0.6
Facial expression	1.91±0.2	1.11±0.14	0.97±0.14	0.09
Resting tremor	8.36±1.44	1.52±0.64	0.83±0.46	0.05
Action tremor	3.05±0.62	0.55±0.24	0.25±0.16	0.02
Rigidity	11.02±1.28	3.44±0.88	1.41±0.68	0.000
Finger tap	4.66±0.62	1.66±0.42	1.25±0.52	0.02
Hand movement	4.02±0.62	1.41±0.48	1.02±0.48	0.004
Rapid alternating movement	3.88±0.68	0.83±0.34	0.55±0.34	0.03
Leg agility	5.02±0.68	2.8±0.56	2.25±0.66	0.07
Arising from chair	1.8±0.4	0.19±0.14	0.16±0.16	0.71
Posture	1.97±0.24	0.83±0.18	0.75±0.2	0.41
Gait	2.13±0.32	0.75±0.22	0.63±0.24	0.25
Postural stability	2.08±0.32	1.02±0.2	1±0.22	0.74
Body bradykinesia	2.58±0.32	0.91±0.24	0.63±0.24	0.02

Values are expressed as means±2SEM
**p value refers to the comparison between preoperation, on-medicaion and postoperation, on-medication conditions.*

procedure performed in Iran. There was no implant-related complication in any of our patients.

Medication
Regarding the medication used, mean L-dopa equivalent doses showed significant decline from 1296 ± 224 mg/d before surgery to 783 ± 87 mg/d after DBS ($p<0.001$).

DISCUSSION

As a target of ablation therapy, the globus pallidius (GP) has for a long time been the standard in the management of parkinsonian syndrome.[6-9] However, serious adverse effects, such as visual impairment and behavioral and cognitive disturbances necessitate probing for more effective procedures.[10-12] Introduction of deep brain stimulation (DBS), made it possible to reduce many of these complications as it is non-destructive and reversible. Stimulation of STN appeared to be more effective than GP because of its smaller size and more homogenous structure.[24]

We have evaluated the short term results of bilateral STN-DPS on motor condition and drug consumption in advanced Parkinson cases. The study benefited from acceptable sample size37 comparing with other studies that had enrolled 5 to 50 patients. The age range of individuals in the study was consistent with advised suitable one for undergoing the procedure because people over 70-75 do not yield favorable response.

A significant effect was observed on motor function at 6 months follow-up. This improvement was calculated as over 60% in total score of UPDRS III and in items related to rigidity, bradykinesia, action tremor, finger tap, rapid and alternating hand movement as well. All of individuals were assessed on medication with the stimulator on after surgery. We also observed a considerable reduction in the frequency and severity of motor fluctuations, the symptom contributes to major preoperative functional limitations. This favorable improvement in advanced disease is crucial for the patients and often represents the main objective of the procedure.

Considerable lower need for anti-parkinsonian medication by 40% while using the stimulator was another positive finding that, consequently, can result in antidyskinetic

effect. The average medication reduction in the prior studies was reported 57.8%.[20-24]

As mentioned in other studies it was not possible to blind investigators or patients. They often became aware of the on/off status of the stimulation because of the symptom relief or because of symptoms that occurred at the onset of stimulation, like parasthesia. Severe complications of the procedure are infrequent in reported surveys. The most common problem is, though mostly transient, deterioration of the patients' psychiatric state. Similar observations have already been reported for ablative operations as well as for stimulation procedures in both the GPi and STN. Therefore, careful patient selection and preoperative neuropsychological testing over an extended period are of utmost importance.

Finally, our study along with other studies support the beneficial outcome of STN-DBS in improving parkinsonian motor signs and reducing medication and supports its utilization in selected target for the treatment advanced stages of the disease. However, long term follow-ups are needed for complete assessment.

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REFERENCES

1. Koller WC, Pahwa R, Lyons KE, Albanese A. Surgical treatment of Parkinson's disease. *J Neurol Sci* 1999; **167**:1-10.
2. Krack P, Poepping M, Weinert D, Schrader B, Deuschl G. Thalamic, pallidal, or subthalamic surgery for Parkinson's disease? *J Neurol*. 2000;**247(Suppl 2)**:II122- II134.
3. Baron MS, Vitek JL, Bakay RA, et al. Treatment of advanced Parkinson's disease by posterior GPi pallidotomy: 1-year results of a pilot study. *Ann Neurol* 1996;**40**:355-66.
4. Uitti RJ, Ahlskog JE, Maraganore DM, Muenter MD, Atkinson EJ, Cha RH, et al. Levodopa therapy and survival in idiopathic Parkinson's disease: Olmsted County project. *Neurology* 1993;**43(10)**: 1918-26.
5. Olanow CW, Hauser RA, Gauger L, Malapira T, Koller W, Hubble J, et al. The effect of deprenyl and levodopa on the progression of Parkinson's disease. *Ann Neurol* 1995;**38(5)**:771-7.
6. Laitinen LV, Bergenheim AT, Hariz MI. Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease. *J Neurosurg* 1992;**76**:53-61.
7. Ghika J, Ghika-Schmid F, Fankhauser H, et al. Bilateral contemporaneous posteroventral pallidotomy for the treatment of Parkinson's disease: neuropsychological and neurological side effects. Report of four cases and review of the literature. *J Neurosurg* 1999;**91**:313-21.
8. Linazasoro G, Guridi J, Rodriguez MC, et al. Surgery of the subthalamic nucleus in Parkinson's disease. *Rev Neurol* 2000;**30**:1066-72.
9. Starr PA, Vitek JL, Bakay RA. Ablative surgery and deep brain stimulation for Parkinson's disease. *Neurosurgery* 1998;**43**:989-1013.
10. Rowe JG, Davies LE, Scott R, Gregory R, Aziz TZ. Surgical complications of functional neurosurgery treating movement disorders: results with anatomical localisation. *J Clin Neurosci* 1999;**6**:36-7.
11. Trepanier LL, Kumar R, Lozano AM, Lang AE, Saint-Cyr JA. Neuropsychological outcome of GPi pallidotomy and GPi or STN deep brain stimulation in Parkinson's disease. *Brain Cogn* 2000;**42**:324-47.
12. Hariz MI. Current controversies in pallidal surgery. *Adv Neurol* 1999;**80**:593-602.
13. Gross RE, Lozano AM. Advances in neurostimulation for movement disorders. *Neurol Res* 2000;**22**:247-58.
14. Barcia-Salorio JL, Roldan P, Talamantes F, Pascual-Leone A. Electrical inhibition of basal ganglia nuclei in Parkinson's disease: long-term results. *Stereotact Funct Neurosurg* 1999;**72**:202-7.
15. Bejjani B, Damier P, Arnulf I, et al. Pallidal stimulation for Parkinson's disease. Two targets. *Neurology* 1997; **49**:1564-9.
16. Davis KD, Taub E, Houle S, et al. Globus pallidus stimulation activates the cortical motor system during alleviation of parkinsonian symptoms. *Nat Med* 1997;**3**:671-74.
17. Pollak P, Benabid AL, Gross C, Gao DM, Laurent A, Benazzouz A, et al. Effects of the stimulation of the subthalamic nucleus in Parkinson disease. *Rev Neurol (Paris)* 1993;**149**:175-6.
18. Levesque MF, Taylor S, Rogers R, Le MT, Swope D. Subthalamic stimulation in Parkinson's disease. Preliminary results. *Stereotact Funct Neurosurg* 1999;**72**: 170-3.
19. The Deep-Brain Stimulation for Parkinson's Disease Study Group. Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. *N Engl J Med* 2001; **345(13)**:956-63.
20. Kumar R, Lozano AM, Kim YJ, Hutchison WD, Sime

E, Halket E, et al. Double-blind evaluation of subthalamic nucleus deep brain stimulation in advanced Parkinson's disease. *Neurology* 1998;**51(3)**: 850-5.
21. Vingerhoets FJ, Villemure JG, Temperli P, Pollo C, Pralong E, Ghika J. Subthalamic DBS replaces levodopa in Parkinson's disease: two year follow-up. *Neurology* 2002;**58(3)**:396-401.
22. Krack P, Batir A, Van BN, Chabardes S, Fraix V, Ardouin C, et al. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med* 2003;**349(20)**: 1925-34.
23. Visser-Vandewalle V, van der LC, Temel Y, Celik H, Ackermans L, Spincemaille G, et al. Long-term effects of bilateral subthalamic nucleus stimulation in advanced Parkinson disease: a four year follow-up study. *Parkinsonism Relat Disord* 2005;**11(3)**:157- 65.
24. Rodriguez-Oroz MC, Obeso JA, Lang AE, Houeto JL, Pollak P,Rehncrona S, et al. Bilateral deep brain stimulation in Parkinson's disease: a multicentre study with 4 years follow-up. *Brain* 2005;**128**:2240-9.
25. Kumar R, Lozano AM, Montgomery E, Lang AE. Pallidotomy and deep brain stimulation of the pallidum and subthalamic nucleus in advanced Parkinson's disease. *Mov Disord* 1998;**13**:73-82.