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Early outcome of subthalamic nucleus deep brain stimulation (STN-DBS) in advanced parkinson disease in first trial of Iranian patients

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Abstract

Background: To improve the debilitating features of Parkinson disease (PD) different 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 first trial of Iranian patients.

Methods: Thirty-seven consecutive patients with advanced Parkinson disease with poor response 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 subscores in three measurements performed as 1) preoperative off-medication, 2) preoperative on-medication and 3) six months postoperative on stimulation and on medication. Reduction in drug consumption was assessed with regard to administered doses of L-Dopa before and after surgery in stable states.

Results: 26 men and 10 women with mean age of 50 years were evaluated (one person expired before 6-month follow-up). Mean total scores of UPDRSIII were calculated as 5.2±54.52, 2.88±18.22 and 3±12.8 in three measurements, respectively (p=0.003). PostHoc analyses showed significant improvement among all measurements. Analysis of subscores also revealed significant amelioration in rigidity, resting tremor, hand movement, leg agility, finger tap and rapid alternating movement in on-medication phases of pre- and post-operation (all with $p<0.01$). The mean administered L-Dopa were224±1296 mg/d and 174±782 mg/d before and after surgery, with significant decline ($p<0.001$) in administered L-dopa dose.

Conclusion: The results indicate that bilateral STN-DBS can lead to significant short-term improvement of the motor symptoms especially in some debilitating symptoms such as rigidity and tremor in advanced PD. It also accompanies with remarkable reduction in needed doses of drugs. The findings support other studies with similar follow-up interval; however, continuous evaluations are needed for long-lasting effects.

Keywords: STN-BDS, advanced Parkinson disease, Iranian patiants

Introduction

To improve the debilitating features of Parkinson disease (PD), surgery has been performed on patients suffering from the disease in the early 19th century [1]. Lesions of the thala-

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	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. All other comparisons were significant.

Table1. Scores and subscores of UPDRS III in three measurements of preoperative off-medication, preoperative on-medication and six months postoperative on medication.

mus and pallidum had a good effect on tremor and rigidity [2,3]. Then advent of oral levodopa therapy led to a drastic reduction in the number of surgeries performed on PD patients with additional advantage of improving akinesia. However, after a few years complications associated with 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 contra lateral tremor, rigidity, and, dyskinesias [6-9] . It 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]. The procedure was performed over 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 with poor response 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 that applied the procedure for advanced Parkinson disease. Here we will report 6-month follow-up of patients regarding their motor function and drug administration.

Methods

Population

From patients with severe idiopathic Parkinson disease 37 consecutive individuals 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 was performed for the first time in Iran.

Individuals were included in case of having

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>30% improvement in levodopa challenge test. We excluded patients with significant psychiatric or behavioral 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

The applied procedure is described in detail somewhere else. To be brief, stereotactic MRI imaging was applied to provide direct visualization of subthalamic nucleus. Tetra polar 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 permanent lead. We placed subcutaneous pulse generator in the pectoralis major muscle after few days under general anesthesia. During the next week programming of th pulse generator was done by the neurologist.

Clinical evaluation

Motor performance was evaluated using the UPDRS part III checking items like 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, and each scored with 0 to 4. Lower scores reflected better performances. Preoperative UPDRSIII assessments were also 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 used their medication continuously.

Medication

A stable level of the L-Dopa maintained for at least 2 months prior to surgical exploration as preoperative medication dose. 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 evaluation after surgery.

Statistical analysis

Descriptive analysis of data with normal distribution is presented as means and standard deviations. The UPDRS III total score and items' subscores in two pre-operative and 6 -month follow-up measurements were compared respectively using repeated-measure ANOVA. For analysis of dichotomous evaluations like drug doses before and after surgery paired t-test was applied. A p-value <0.05 was considered to be statistically significant. All data were analyzed by SPSS version 15 (SPSS Inc., Chicago, IL, USA).

Results

Thirty seven patients (26 Male and 10 female) with advanced Parkinson disease underwent STN-DBS surgery and one died of myocardial infarction before discharge. All other remaining patients were included in the study to evaluate 6-month follow-up. Mean age of patients was 50.08±3.04 ranging from 32 to 72 years. The mean duration from beginning of symptoms at the time of surgery was 11.28±1.88 years. Bilateral approach of STN DBS was applied for all patients.

The pre-operative UPDRS III scores of off- and on-medication measurements were 54.52±5.4 and 18.22±2.88, respectively. Postoperative score was yielded 12.8±3.14 that showed significant difference comparing with both preoperative scores ($p<0.001$). Analysis of UPDRS III subscores in two preoperative measurements revealed significant improvement in all items after the L-Dopa consumption ($p<0.05$). Comparison of findings from two on-

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medication phases revealed when DBD was performed significant alleviation in rigidity, resting 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 procedure performed in Iran. There was no implant-related complication in any of our patients.

Medication

Regarding the medication used, the 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

In ablative therapy, the globus pallidius (GP) has for a long time been the standard target in the management of parkinsonian syndrome [6-9]. However, serious adverse effects, such as visual impairment and behavioral and cognitive disturbances necessitated 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 size (37) 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 over 60% in total score of the 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 antiparkinsonian medication by 40% while using the stimulator was another positive finding that, consequently, can reduce the dyskinetic effect of drugs. The average medication reduction in the prior studies was reported 57.8% [20-24].

To compare these results with other studies issues such as patients' baseline characteristics, duration of follow-up and the kinds of evaluated items should be considered. Our findings as short-term follow-up results are mainly consistent with what were reported by previous studies regarding corresponding items.

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 occur at the onset of stimulation, like paresthesia. Severe complications of the procedure are infrequent in reported surveys. The most common problem is, though mostly transient, deterioration of the patients' psychic 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 reduc-

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ing 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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