The Effects of Bilateral Subthalamic Nucleus Stimulation on Cognitive and Neuropsychiatric Functions in Parkinson's Disease: A Case-Control Study

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ABSTRACT

Introduction: Parkinson's disease is one of the most disabling diseases which by electrode implantation and stimulation of subthalamic nucleus (STN), much progress has been made in the treatment of drug resistant patient. This new method of neurosurgery may have some neuropsychological side effects on the patients. The main aim of this study is to evaluate the effects of this kind of treatment on the different neuropsychological aspect of patients.

Methods: The case-control study designed for comparing two groups of patients with Parkinson's disease. Thirty patients, who underwent electrode implantation and Deep Brain Stimulation (DBS), compare with 60 patients treated with antiparkinson's drugs. These two groups matched in age, sex, Parkinson's disease duration and Parkinson's severity scores. Measurements: the UPDR scale was used to assess the severity of the Parkinson's severity. Beck Depression Inventory questionnaire (BDI) and Hamilton Anxiety Rating Scale questionnaire (HARS) were used to evaluate the depression and anxiety consequences of DBS.

Mini Mental Status Examination (MMSE) and Clock Drawing Test (CDT) were used to evaluate the cognitive and executive function of the study subjects.

Results: patients with STN stimulation showed lower level of anxiety and depression, however, the cognitive status were more deteriorated in study subjects than control group.

Discussion: Patient with DBS surgery have to be followed up for neuropsychiatric symptoms particularly for the cognitive deterioration in long term period.

1. Introduction

Parkinson's disease is one of the most prevalent movement disorders throughout the world. In recent years, considerable pharmacological and surgical progress has been made in the treatment of this disabling disease. The major sites of dysfunction in Parkinson's disease are the subthalamic nucleus (STN) and substantia nigra (SN), which are two components of the basal ganglia (BG)(Joseph J & Tolosa, 2007; Sadock B, Sadock J, & A, 2009; Sadock B, Sadock J, & V, 2007). The loss of dopaminergic neurons in the SN results in hypokinetic symptoms secondary to overactivity of the STN and globus pallidus (GPi) via the indirect pathway and hyperkinetic movement caused

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by overactivity of the direct pathway(Joseph J & Tolosa, 2007; R.F & I, 2005; Sadock B et al., 2007). Subthalamic deep brain stimulation (DBS) is one of the most important interventions in functional neurosurgery and has transformed the treatment of advanced or drug resistant Parkinson's disease(Baltuch GH & MB, 2007). STN as a driving source of the BG plays an important role in the pathogenesis of Parkinson's disease(Heo et al., 2008). In addition to the importance of this structure in motor coordination, the STN regulates cognition and emotion; stimulation of this site can cause emotional or cognitive changes(Temel, Blokland, Steinbusch, & Visser-Vandewalle, 2005). Despite the effect of STN stimulation on controlling the motor symptoms of Parkinson's disease, the effects of this procedure on cognition and mood are not well-established. One study has shown that, three years after surgery, two cognitive variables became worse (category fluency and total score of fluency). Apathy and thought disorders were also worsened. The major behavioural changes documented in this study includes two transient aggressive impulsive episodes, one suicide, four suicide attempts, one case of permanent apathy, one case of transient severe depression, four psychoses (one permanent) and five cases of hypomania (one permanent)(Funkiewiez et al., 2004). The location of the electrode may have an impact on mood changes. In one case report, right DBS alone elicited several episodes of acute depressive mood changes. The electrode on the left was within the inferior STN, whereas the right electrode was marginally superior and lateral to the intended STN target within the fields of Forel/zona inserta(Stefurak et al., 2003). Sometimes, this may cause manic symptoms or suicidal behaviour (Burkhard et al., 2004; Herzog et al., 2003). Although DBS deteriorates cognitive function and mood disorders such as depression, anxiety or improving in these symptoms; important challenges persist in the development of this type of treatment. In recent years, some studies have been designed to address the effects of DBS on cognitive function and mood changes (Benabid, 2003; Chan et al., 2009; Fields et al., 2003; Peron et al., ; Rothlind, Cockshott, Starr, & Marks, 2007; Saint-Cyr, Trepanier, Kumar, Lozano, & Lang, 2000; Schneider et al., 2003; Temel et al., 2006).

Deep brain stimulation by electrode neurosurgery is a new technique for the treatment of Parkinson's disease and some other neuropsychiatric disorders such as obsessive compulsive disorder,(Abelson et al., 2005) TIC disorder(Flaherty et al., 2005)and refractory depression(Mayberg et al., 2005). This method of treatment has recently been initiated for the treatment of Parkinson's disease in Iran. DBS surgery is one of the most expensive surgeries, and is partially been paid by the Iranian Ministry of Health. Rasool Akram Hospital in Tehran, the capital city of Iran, is the only academic centre in Iran in which DBS surgery has been conducted science now. Despite being a pioneering centre in the surgery of patients with Parkinson's disease, this is the first study performed to study the neuropsychological and cognitive effects of DBS carried out at this facility. Our purpose is to evaluate the effects of DBS on the psychiatric complaints (anxiety and depression) and cognitive function of these patients.

2. Methods

2.1. Study Design

We used a case-control design in which patients with Parkinson's disease treated with the DBS technique were compared with patients suffering from Parkinson's disease who were treated with antiparkinson's drugs. In all of the case group the electrodes located bilaterally in the STN during stereotactic surgery.

This case-control study was performed at the Rasool Akram Hospital in Tehran, Iran. At the beginning of this study, only 30 study subjects were with Parkinson's disease periodically attended the clinic after surgery in the study centre. The mean time after DBS surgery in these group were 31.43 months, After completion of the recruiting phase for the case subjects, two control subjects were selected for every case subject; therefore, 60 control subjects were recruited. The control group was selected by matching subjects according to age (±2 years), gender, duration of Parkinson's disease (±2 years) and the severity of disease according to the UPDR scale (± 5 points). The control group samples had not been candidate for DBS due to several possible reasons like preferring medication instead of surgery, fear of surgery, financial problem and lack of insurance support.

2.2. Surgical and MRI Procedures

The Leksell-G Stereotactic head frame was fixed to the patient's skull under local or general anesthesia parallel to the orbitomeatal plane. Then the patient was transferred to MRI suite, where special sequences were obtained on a 1.5 Tesla machine (Philips Gyroscan). The series of images were taken pre-operatively included: 3-dimentional MR T1-weighted and MR T2-weighted coronal and axial images and inversion recovery (IR) without any gantry tilt.

The localization of the initial STN (Subthalamic nucleus) target was calculated by stereotactic software (Ste-

reonauta Plus, Madrid, Spain Version II) on coronal and axial T2-weighted images (the center of hypointensity of STN on T2 Weighted MRI image) acquired orthogonally to Anterior Commissure-Posterior Commissure axis (AC–PC axis) crossing the anterior limit of the Red Nucleus. Then the initial target coordinates (X, Y, Z) were plotted on the T1-weighted image with contrast to find a safe trajectory for insertion of DBS electrode (avoiding intracranial vessels or ventricles).

In the operating room, five microelectrode trajectories were inserted into the brain and simultaneous electrophysiological monitoring was performed. After finding the optimal location for stimulation based on the length of STN recorded, effects and side-effects to acute macro stimulation, the permanent leads were implanted and fixed.

It's demonstrated that the degree of clinical improvement after DBS largely depends on the accuracy of electrode placement. The small size, ovoid shape, and oblique disposition of the STN and the individual variability in the STN situation are responsible for spatial inter-individual fluctuations of the real patient's target, which might significantly differ from the theoretical statistical target.

For calculating the location of the STN, a line drawn from the anterior commissure (AC) to the posterior commissure (PC) and calculates the mid commissure point (MCP) (Mansour ParvareshRizi & Bakhti., 2010), then DBS and MRI parameters including the target coordinates (X, Y, Z) and the distances from MCP to the center of STN in all three axes, on both sides were calculated for each patient. According to this method the anatomic location of STN identified from MCP. The average locations are About 11.05 mm for X axis, 3.18mm for Y axis and 3.68 for Z axis.(Mansour ParvareshRizi & Bakhti., 2010)

2.3. Measurements

All study subjects provided fully informed consent. The study instruments included a demographic questionnaire, the Hamilton Anxiety Rating Scale (HARS) for detecting the severity of anxiety(Hamilton, 1959), the Beck Depression Inventory (BDI) for detecting depression symptoms and severity, the Mini Mental Status Examination (MMSE) for evaluating cognitive function. The Clock Drawing Test (CDT) with the Mendez scoring method was completed by self-report(Mendez, Ala, & Underwood, 1992), as well as by interviewing and examining the cognitive function of the subjects. The past psychiatric history of all patients was investigated and recorded on the demographic questionnaire. All instruments were completed when the study subjects were in the "on" phase. ("on" phase in control subjects, means taking medication and "on" phase in case subjects means the DBS device was on)

The severity of disease was measured by the UPDR scale at two points. The first was in the "off" condition of drug treatment in both groups. The score under these conditions was registered in the patient's medical documents and used in this study. The second assessment, which was conducted by the researcher, was in the "on" condition when the surgery had been performed for the DBS group with concurrent drug treatment and in the control group when subjects were taking medication at the recommended dose.

This study was approved by the Ethics Research Committee of the Tehran Psychiatric Institute.

The authors declare no conflicts of interest in conducting this study.

3. Results

We enrolled 90 subjects in this study, with 30 patients in the case group (Parkinson's disease with DBS therapy) and 60 patients in the control group (Parkinson's disease with pharmacotherapy). The mean time after DBS surgery in these group were 31.43 months (minimum duration was 3 months and maximum duration was 96 months). (Table 1)

Table 1 shows the demographic characteristics of the participants and the severity of Parkinson in both groups in "on" and "off" condition. The study sample, in both the case and control groups, was matched for age, gender, duration of disease and severity index.

The Parkinson severity in "off and on" conditions were 54.73 and 12.93 in DBS group (case group); 55.66 and 14.8 in drug group (control group) which shows the efficacy of both intervention, however, the difference between two groups were not significant in either condition. (Table 1)

Since the HARS, CDT and MMSE results were not normally distributed in our sample (Table 2), we used the nonparametric Mann Whitney U test for comparing scores.

In the assessment of mood and anxiety, the mean ranks of the HARS scores were 40.75 and 47.88 in the case and control groups, respectively (P = NS). The mean ranks of the BDI scores were 43.42 and 46.54 in the case

Table 1. Demographic features of the study sample (n=90).

	Case (n=30)/ Control (n=60)	Min	Max	Mean (SD)	Sig	T	Df
Age	DBS	40	71	51.23 (7.15)	0.879	0.284	NS
	DRUG	36	67	50.78(7.04)			
Sex	DBS	Male = 25 (83.3%) Female = 5 (16.7%)			0.687	0.203	NS
	DRUG	Male = 51 (85 %) Female = 9 (15%)					
Parkinson Duration	DBS	7	16	10.65(2.85)	0.708	1.524	NS
	DRUG	5	16	9.67(2.90)			
UPDRS on	DBS	5	23	12.93(4.52)	0.786	-1.781	NS
		7	30	14.80(4.76)			
UPDRS off	DRUG	34	92	54.73(13.50)	0.263	-0.351	NS
		34	88	55.66(11.03)			
DBS duration (months)	Case	3	96	31.43			

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The Mann Whitney U test showed no significant difference in the HARS scores between patients with DBS and those on pharmacotherapy (Mann Whitney U = 757.5, z = -1.22). No significant difference was seen in the BDI scores in the two groups (Mann Whitney U = 837.5, z = -0.536).

In the assessment of cognitive function, the mean ranks of the MMSE scores were 39.22 in the case group and 48.64 in the control group (p = 0.096). For the CDT scores, the mean rank was 36.33 in the case group compared with 50.08 in the control group (p = 0.015) (Table 4).

Table 2. Tests of normality for study variables.

	UPDRS off	UPDRS on	HARS	BDI	MMSE	Clock Test
Mean ±SD	55.36±1.18	14.18±4.74	12.92±7.03	13.46±12.45	28.26±1.87	17.86±2.92
K.S. test P. value	0.145	0.233	0.016	0.140	0.001	0.000

K.S: Kolmogorov-Smirnov , SD: Standard Deviation

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Table 3. Mann Whitney U test results on neuropsychological features in DBS and pharmacotherapy cases.

	Case/Control	N	Mean ± SD	P.value **
HARS	DBS(Case)	30	11.50 ± 5.57	0.222
	Drug(control)	60	13.63 ± 7.6	
BDI	Case	30	12.8 ± 7.34	0.592
	Control	60	13.8 ± 7.25	

*Number ** Mann Whitney U test

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Table 4. Mann Whitney U test results on cognitive status in DBS and pharmacotherapy cases.

	Case/Control	N	Mean ± SD	P.value **
MMSE	Case	30	27.5 ± 2.55	0.096
	Control	60	28.63 ± 1.29	
Clock test	Case	30	16.7 ± 4.55	0.015
	Control	60	18.43 ± 1.3	

*Number ** Mann Whitney U test

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In the assessment of neurocognitive function, the Mann Whitney U test showed a significant difference between the DBS and pharmacotherapy groups in terms of the CDT scores ($p<0.05$, $z = -2.428$, Mann Whitney U = 625.000), but the test showed no significant difference in the MMSE scores between the two groups (Mann Whitney U = 711.500, z = -1.667).

For evaluating the past history of mental illnesses, the study samples of the case and control groups were divided into two groups, with and without past psychiatric history. There was no significant difference ($\chi 2 = 1.4$, df = 1).

4. Discussion

This study was carried out on subjects within 30 months of performing DBS using a case-control study design.

The main findings of this study showed that psychiatric problems, including depression and anxiety, do not occur to a significantly greater extent in patients treated with DBS compared to those given pharmacotherapy. Nevertheless, cognitive changes were detected after DBS intervention. The MMSE scores were not different significantly between the two groups, but the CDT score was increased in the DBS group.

Although the severity of anxiety and depression was not different, the scores were lower in the DBS group. Increasing the sample size may make it possible to detect differences. In previous case report studies, DBS (subthalamic electrode implementation) was associated with depressive symptoms and suicidal ideation (Berney et al., 2002; Stefurak et al., 2003). In a study carried out by Funkiewiez (2004), the results showed that, after three years, mood improved and cognitive function showed no significant changes (Funkiewiez et al., 2004). Deep brain stimulation treatment bilaterally in the globus pallidus internus substantially improved symptoms of depression as measured by the Hamilton Rating Scale of Depression(Kosel et al., 2007). Chronic stimulation of white matter tracts adjacent to the subgenual cingulate gyrus has resulted in marked improvement in chronic and refractory depression(Mendez et al., 1992). Therefore, the current controversy could be accounted for partly by the location of the electrodes implemented in deep brain tissues(Stefurak et al., 2003).also whether the electrode located in the dorsal or ventral part of STN may associated with different effects on motor symptoms and affect, dorsal stimulation of STN may cause less variable motor response and more improvement in UPDRS motor rating, this effect likely achieved by selectively stimulation and modulation of sensorimotor territory of STN or afferent projection. Ventral stimulation of STN may change limbic function and associated with more positive affect and emotions so whether the electrode more contact with the ventral or dorsal part of STN, may cause different effect on mood and affect of patients.(Greenhouse et al.)

In the assessment of cognitive function, the effect of subthalamic DBS was not significant, although lower scores were seen in the MMSE in the DBS group than in patients treated with pharmacotherapy. This may have been due to the high degree of cortical appraisal in the MMSE. DBS in the STN does not involve cortical areas; therefore, MMSE scores may not be affected by the DBS procedure. However, it could be speculated that the sample size was insufficient and that increasing the study sample size may decrease MMSE scores in the DBS group.

On the other hand, the CDT scores in the DBS group were lower than in the pharmacotherapy group, and this difference was significant. It is reasonable that, in the DBS group, performing some procedures involving basal ganglia structures may have revealed some cognitive impact mainly related to subcortical areas and executive functions. The CDT evaluates subcortical cognitive functions, and this result could be reasonable, even with the rather small sample size used in this study (Nair et al., 2010; Peters & Pinto, 2008; Pinto & Peters, 2009).

In a study performed in Texas, an association was also detected between the location of the tip of the electrode and cognitive and memory functions (York, Wilde,

Simpson, & Jankovic, 2009). Kosel et al. showed that, after 15 months of follow-up, DBS in the STN and DBS in the GPi were associated with reduced cognitive abilities such as verbal fluency and working memory(Kosel et al., 2007). DBS surgery performed for essential tremor resulted in a decrease in semantic memory and visual memory(Baltuch GH & MB, 2007).

Regarding to neurocognitive squeal, different anatomical locations have been tried. Some research showed that cognitive processing was lower in STN stimulation compared with GPi stimulation; nevertheless, there were no significant differences in motor functions between GPi and STN stimulation. Therefore, in addition of motor outcomes, the neurocognitive results should be considered in surgery procedure(Follett et al., 2010), but the other research showed that long term motor efficacy of STN implants has been up to 8 years, compare to 5.5 years for GPi implants (Albanese & Romito) and no difference in mood and cognitive outcome of these two methods (GPi versus STN).(Okun et al., 2009; Okun et al., 2003; Weaver et al.)

It can be concluded that DBS surgery could have a neuropsychiatric and cognitive impact which must be followed by the management team. Appropriate medical and non-medical intervention should be considered in these cases.

Because of the limited number of people candidate for surgery and DBS, we couldn't assess subject before and after DBS and it takes long period of time.

It didn't possible to turn OFF device in case group for neurocognitive assessment in OFF status because of moral reason.

In subsequent studies, a more powerful study design with a structural interview for axis one diagnosis and evaluation (According to DSM-IV TR) and a completed neuropsychology battery will be employed to evaluate the long-term impact of DBS surgery.

Regarding to socio- economic situation of the two groups, it could be mentioned that the case subjects may have been in higher level which could afford for the expensive DBS surgery, however, it is not clear that the socio-economic conditions could have any significant effect on the neuropsychiatry impact of DBS intervention.

6. Authors Contribution

Reza Mahdavi designed and conducted the study, data collection and drafting the article. Seyed Kazem Malakouti contribute the conception and designed the study and revised critically the article. Gholam Ali Shahidi contribute the design and revised the article. Parvaresh contribute the conception and reviewed the article.

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