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Surgical Treatment of Parkinson's Disease: A Clinical Prospective Study with Six Years Follow up

Moneer K. Faraj *MBChB, FICMS, FICS*

Dept. of Surgery, College of Medicine, Baghdad University

Abstract

Background Deep Brain stimulation is well accepted now as amethod for treating refractory parkinsons disease.

Objective To describe deep brain stimulation in Iraq, emphasize the technically demanding procedure and to discuss the results on the patients after six years of follow up.

Methods A clinical prospective study of 8 patients with Parkinson's disease underwent deep brain stimulation surgery in the Neurosciences Hospital. We performed 18 multiple stages operations from October 2007 to June 2008. The procedure begins with proper selection of patients, pre operative radiological studies, planning for targeting the subthalamic nucleus, the operation stage and the programming stage, which usually starts one-week post operatively.

Results One patient developed subarachnoid hemorrhage, another one have miss targeting and required retargeting surgery. A part from these complications all the patients had satisfactory outcome in controlling their symptoms during the six years follow up period.

Conclusion Deep brain stimulation is indicated for the treatment of refractory Parkinson disease. However it needs a well skilled personnel working as a team. The future of deep brain stimulation is remarkable as the list of indications is continually increasing to include other disease modalities.

Key words Parkinson's disease, deep brain stimulation, functional neurosurgery.

List of abbreviation: PD = Parkinson's disease, DBS = Deep Brain Stimulation, GPi = Globus Pallidus Internus, STN = Sub thalamic nucleus, MRI = magnetic resonance imaging, CT = computed tomography, IPG = Implantable Pulse Generator, AC= anterior commissure, PC = posterior commissure.

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease. The main clinical features composed of resting tremor, bradykinesia and rigidity. These tend to occur early in the course of the illness; postural instability, loss of balance and freezing of gait are later features [1-4]. As PD progress, intractable disability is commonly caused by medically unresponsive axial symptoms particularly gait and postural impairment, dysphagia, dysphonia and cognitive decline [3-5].

Deep brain stimulation (DBS) has become an accepted treatment for medically refractory PD. Those includes all the patients whom not adequately controlled with medications, disability resulting from hypokinetic fluctuations, dyskinesia and/or tremor [6]. It improves PD motor symptoms proportionally to the pre-operative response to levodopa; the improvement of motor disability allows a significant reduction in dopaminergic therapy with consequent regression of drug-related dyskinesia [7,8].

Both Globus Pallidus Internus (GPi) and Sub thalamic nucleus (STN) stimulation have shown similar efficacy rated. However the literature demonstrates a trend that STN stimulation may be more effective in managing the symptoms of

PD. The Choice of the STN over the GPi is often based on institutional experiences, surgical and programming expertise and preferences [9-11].

Method

Patients Selection

In this clinical prospective study, eight patients were selected in the period from October 2007 to June 2008 to perform the surgery. They were evaluated with certain inclusion criteria; the patient must pass it before accepting him to this therapy (Table 1). We performed 21 operations for 8 patients with PD. Two patients completed the whole procedure in one session, two patients completed the surgery in two sessions and four patients had three sessions.

Table 1. Inclusion and exclusion criteria for deep brain stimulation

Inclusion Criteria for Surgery/DBS [13]	Exclusion Criteria for Surgery/DBS [14]
1. Good general health 2. "Normal" cognitive and affective functions 3. Motor disability 4. Failure of all drug strategies 5. Good response to L- Dopa drug 6. Good level of functioning when "on" Brain MRI in the normal range	1. Multiple medical complications 2. Dementia, severe frontal lobe dysfunction, severe depression 3. No adequate drug trials 4. Poor levodopa response 5. Disability arising from levodopa-unresponsive symptoms 6. Significant MRI abnormalities

Radiological Studies

These studies include pre-operative magnetic resonance imaging (MRI), head frame fixation with computed tomography (CT) or MRI studies and intraoperative C- arm studies. New set of MRI studies must be done. These ideally be done with 1.5 tesla closed MRI. They must have certain requirements to be accepted for the software of the planning workstation (e.g. frame link of Medtronic or surgiplan of Elekta) like the square image, no overlap, equidistance, no space, no compression, real image (no scout), no gantry tilt, no head tilt, and maximum slice thickness 2 mm

Head Frame Fixation

By using the Leksell Stereotactic Frame System of Elekta. The fixation is done routinely in the radiological department. Taking axial 2 mm thickness volumetric scans (from the hard palate to the vault). These sets of images will not be used for the detection of the target; it will be used by the software program to determine the values of X (medial-lateral), Y (anterior-posterior), Z (superior-inferior) of the STN. We also perform the MRI images with the frame and apply fusion with the frameless images, but the image distortion with the CT-images is much less than with the MRI. During taking these images the surgeon must be sure that all the nine fudicials will appear in the image sections. All these studies should be transferred to the planning workstation (we use Medtronic workstation with frame link software version 4).

Planning For Targeting the STN

After transferring the image data to the workstation, it will be recognized automatically by the software. The images with frame signals will be the registered images and the others will be recognized as the working images. Determining the anterior commissure (AC) and posterior commissure (PC) points is done in the axial T1 MRI images, with simultaneously observing the other sagittal and coronal reconstructed ones. Mark the center of the posterior border of the AC and the center of the anterior border of the PC. The AC-PC line length must be within the acceptable limits (22-26 mm).

The STN will be determined in the T1 images using the indirect method (the formula based equation) i.e., 12 mm lateral to the mid-commissural point, 4mm (2 sections) below and 4mm posteriorly. This will be automatically revealed with single click. We record the values of the x, y, and z of the frame.

In axial views we consider the section with largest diameter of red nucleus. The STN is determined by drawing two tangential lines from the lateral border of the red nucleus and the anterior border of it. The STN is located at a point 2.3 mm away from the lateral border and 2.1mm from the anterior border (Fig. 1).

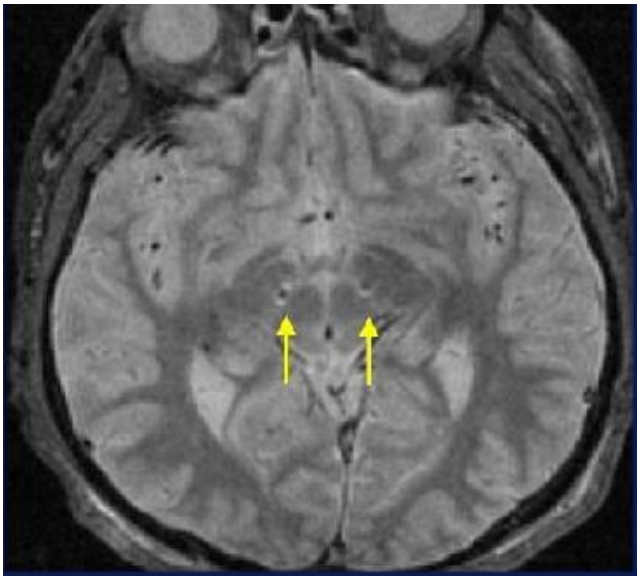

Fig. 1. Targeting the STN in the Axial views

The final agreed reading would be a combination of all the records by taking average reading aiming to include most of the recorded values within a circle of 4 mm diameter, which represents the circle of the 5 microelectrodes that will be used later for recording and stimulation.

We set the entry point just on or 2 cm anterior to the coronal suture (properly visualized through the CT images). It must be sufficiently laterally located to avoid the sinuses and entrance of the trajectory to the cerebral ventricles. In the probe's eye view we should go down to 5 mm below the target area because the recording and stimulation studied will involve these areas too.

Operating Theatre Stage

This stage is composed of application of the arc with the Micro targeting drive, burhole, insertion of the electrodes for recording and stimulation studies, implantation of permanent electrode and implantation of the Implantable Pulse Generator (IPG). The major steps of surgery are done under local anesthesia to check the response and side effects of the stimulation on the patient.

Intraoperative Neurophysiologic studies

Microelectrode recordings during stereotactic procedure for implantation of DBS electrodes in the STN have provided important data about the physiology and pathophysiology of this nucleus in the humans [16,17].

The criteria for identifying the neural activity of STN were the shape of the units, their firing frequency, the response to passive and active limb displacement and the tremor-locked activity [18].

Recording begins at various distances from STN target from several millimeters up to 40 mm.

The maximal length of STN recorded varies from patient to patient and depends also on the approach angles, but ranges from 4.2 to 5.4 mm.

We chose the most reliable electrode, which reveals the site of the STN to start its stimulation. Stimulation begins with examination for baseline resting tremor and rigidity. All the team most commonly performs testing the DBS electrode for efficacy and side effects.

The final position of the permanent electrode is a shared decision of the neurosurgeon and neurologist with the neurophysiologist. The macro electrodes are introduced into the deepest desired location. The cannula with the accompanying electrode of the desired DBS electrode placement is removed and its length is calibrated with the DBS electrode which will be introduced into the brain and remove it's stylet. Finally it is fixed to the burhole fitter slit and cover it with its plastic cover. C – Arm image is

taken to assure no kink occurred along the pathway of the implanted electrode.

The connection of the electrode with the extension wire and the IPG is implanted in the right subclavicular area. This part of the surgery is done under general anesthesia. The patient's preoperative PD regimen should be restarted immediately after surgery to avoid problems with dopaminergic withdrawal. Patients should undergo postoperative CT scans and/or MRI scans to assess the electrode location and intracranial status. Patients can be discharged as early as 24 hours after surgery, depending on their neurological and cognitive status [19].

Programming of the patient starts usually one-week post operatively in order to avoid the period of lesioning effect of the surgery.

Results

We performed 18 operations for 8 patients and the surgery for each patient was individualized, i.e., some patients complete the whole procedure in one session (2 patients) which includes the electrode implantation on both sides and IPG implantation. Others either in two (2 patients) or three (4 patients) sessions with one week interval for electrode implantation and 3 days later for the IPG implantation. This variation in the number of sessions is due to the long duration of the surgery. The average length of the whole sessions is eight hours; seven hours of them are under local anesthesia, so not every patient can withstand this long duration of awakened surgery. The sessions were delayed upon the request of each patient individually.

The final targeting of the STN was determined as in table 2. All the patients showed significant improvement during the intraoperative stimulation studies. The final location of the permanent electrode was determined as the site with maximum response with the least side effects.

All the patients started programming one week following the surgery to avoid the period of lesioning effect (this is a period in which the patient get relief of the symptoms just because of the lesion that was resulted by the electrophysiological studies). The patient then gets regular visits on monthly period to re evaluate for three months and later on every 6 months.We followed the patients for an average of six years. We start the stimulation with Monopolar program and when we need a higher voltage we shift to bipolar programming to try to length the life of the battery. The voltage for all the patients was in a range between 2.0 to 4.5 volts.

Table 2. details of the operative electrode replacement

Patient	Eelctrode		Final targetig	
	Left side	Right side	Left STN	Right STN
1	Anterior	Medial	-2+5	-3+4
2	Medial	Anterior	-3.5+3.5	-2+5
3	Anterior	Medial	-4+3	-2.5+4.5
4	Anterior	Medial	-1+6	-2+5
5	Medial	Anterior	-1+6	-3+4
6	Anterior	Medial	-3+4	-1+6
7	Anterior	Medial	-3+4	-2+5
8	Anterior	Medial	-4+3	-3+4

STN = subthalamic nucleus, - No. = millimeters proximal to the target point, + No. = millimeters beyond the target point. Each permanent electrode has four attachment point for stimulation making 7mm length of active area to stimulate the subthalamic nucleus.

In the follow up period, 4 patients we reduce their medication and the others with the same dose of l- Dopa but with better symptomatic relief (Table 3).

We had one patient developed intravenricular hemorrhage. This enforced us to delay one face of electrode implantation for one month. Another patient developed errors during programming which necessitate retargeting procedure. Six of our patients had to change their IPG because of the end of battery life

Table 3. The followup results over six years period

Patients	Duration of follow up (Months)	Starting mode	Recent mode	Post operative drug dosage (+)
1	75	Monopolar	Monopolar	Reduced 40%
2	72	Monopolar	Bipolar (6 months)	Reduced to 25%
3	70	Monopolar	Bipolar (8 months)	Not changed
4	78	Monopolar	Bipolar (3 months)	Not changed
5	68	Monopolar	Bipolar (8 months)	Not changed
6	62	Monopolar	Bipolar (8 months)	Not changed
7	62	Monopolar	Monopolar	Reduced 40%
8	60	Monopolar	Bipolar (3 months)	Reduced 30%

(+) = The drug reduction in the table is related to the L- Dopa. For all patients the dopamine agonist were reduced but the neuroprotective medications remained unchanged

Discussion

To establish the DBS services in Iraq, many challenges were faced. The time of surgery was challenge per se; our first surgery last for 13 hours but with splitting the operation into 2 to 3 stages and with increment in the learning curve the time reduced to 5-6 hours. Our average time was eight hours. This is close to the readily accepted average time of six hours [19].

As noticed in the results, 50% of our patients had significant reduction in the dose of their medication with significant relief of the tremor, because they were in continuous contact with us for follow up better than the others. Compared with other data, the reduction in the dose was ranging from 20, 35 to 60 % [9,10,20]. The reduction of the medication alone is not the only indicator of the success of surgery but the better control of the symptoms even with the same medication is the main gain to all our patients [20,21].

Those patients who have no change in their dose of medication, they have axial symptoms and postural instability, which is in many literatures, does not respond to STN stimulation as tremor and rigidity [20]. It was concluded that the postural instability usually not relived with the DBS [20-22]. The risk of intracerebral or intravenricular hemorrhage is well recognized in the literatures [20,21]. It is estimated to be 2.5-5% in most centers. It can be avoided by proper planning of the trajectory by using higher resolution MRI imaging like 3 tesla MRI.

In conclusion, DBS is a reliable control measure for PD. It does not affect the fate or progress of the illness. In contrast to the other ablative procedures; DBS is completely reversible that can remove the whole stuff with no permanent lesion to the patient's brain.

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Conflict of interest

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E-mail: drmkfaraj@uod.edu.iq
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