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Clinical outcomes of PD patients having bilateral STN DBS using high-field interventional MR-imaging for lead placement

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Abstract

Objective—Recently, an iMRI-guided technique for implanting DBS electrodes without MER was developed at our center. Here we report the clinical outcomes of PD patients undergoing STN DBS surgery using this surgical approach.

Methods—Consecutive PD patients undergoing bilateral STN DBS using this method were prospectively studied. Severity of PD was determined using the UPDRS scores, Hoehn and Yahr staging score, stand-sit-walk testing, and the dyskinesia rating scale. The primary outcome measure was the change in UPDRS III off medication score at 6 months. DBS stimulation parameters, adverse events, levodopa equivalent daily dose (LEDD), and DBS lead locations were also recorded. Seventeen advanced PD patients (9M/8F) were enrolled from 2007 – 2009.

Results—The mean UPDRS III off medication score improved from 44.5 to 22.5 (49.4%) at 6 months ($p=0.001$). Other secondary outcome measures (UPDRS II, III on medication, and IV) significantly improved as well ($p<0.01$). LEDD decreased by an average of 24.7% ($p=0.003$). Average stimulation parameters were: 2.9V, 66.4*u*s, 154 Hz.

Conclusion—This pilot study demonstrates that STN DBS leads placed using the iMRI-guided method results in significantly improved outcomes in PD symptoms, and these outcomes are similar to what has been reported using traditional frame-based, MER-guided stereotactic methods.

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Keywords

Parkinson's disease; Subthalamic nucleus; deep brain stimulation; interventional MRI

Introduction

Traditionally, deep brain stimulation (DBS) surgery is performed using frame-based stereotaxy and some form of physiologic mapping such as single unit microelectrode recording. Many groups have published data on lead location as determined by postoperative MRI and correlated it with single unit neuronal recordings [1–4], stimulation induced adverse events [5–7], and clinical outcomes [6, 8–15]. As evidenced by the presence of motor-responsive neurons and beneficial clinical outcomes, these papers collectively show that the dorsolateral subthalamic nucleus (STN) corresponds with the motor subterritory of the STN. Furthermore, this subterritory can be well visualized on optimized T2-weighted MRI sequences.

This literature and our own clinical experience served as the basis for the development of a new methodology for STN DBS implantation in Parkinson's disease (PD) patients using purely anatomically-based targeting of the STN and real-time MRI images. Intraoperative MRI is a technique developed in the mid 1990's to allow neurosurgical procedures to be performed within a MRI scanner [16–19]. This provides the opportunity for surgeons to obtain real-time imaging during surgery within a sterile field established in and around the bore of the scanner. Our approach uses a standard diagnostic 1.5T MRI that is located in a radiology MRI-suite rather than a MRI that is located in an operating room, so we refer to this technique as "interventional MRI" instead of "intraoperative MRI."

Interventional MRI-guided DBS (iMRI DBS) placement differs from traditional surgery in several important ways. The entire procedure including targeting, trajectory planning, lead placement and confirmation of lead location takes place within the bore of the MRI scanner. A plastic skull mounted aiming device is used in lieu of a traditional stereotactic frame. Target localization is achieved using real-time anatomic imaging only. No microelectrode recording (MER), macrostimulation or any form of physiologic localization is used. Because of this, fewer brain penetrations are required and the patient can be placed under general anesthesia. Finally, targeting of the STN is done from MR images that are obtained after placement of the burr hole rather than from MR images obtained pre-operatively. This allows the surgeon to account for brain shift that can occur in the cortex and subcortex after dural opening when planning the target within the STN.

In our previous publication we described in detail the technique and application accuracy of this technique [20]. We showed the accuracy of this method, measured by the difference between expected and actual DBS lead tip locations, to be improved over that of traditional, microelectrode-guided surgery using standard frame-based stereotaxy and preoperative MR imaging. We also speculate this technique may lead to more rapid lead implantation and greater patient comfort. In this study we focus on the clinical outcomes of these PD patients after having bilateral STN DBS surgery using the iMRI approach to lead placement.

Materials and Methods

Patients

All consecutive PD patients undergoing bilateral STN DBS using the iMRI method were enrolled in this study. Inclusion criteria were: a diagnosis of idiopathic Parkinson's disease, disease duration > 5 years, development of motor fluctuations and/or dyskinesia, severe

functional impairment despite optimal medical management. Exclusion criteria were: co-morbid conditions that elevate neurosurgical risks, brain MRI showing extensive brain atrophy or small vessel ischemic disease, pregnancy, or ongoing severe mood or psychiatric symptoms.

Study design and clinical rating scales

All participants underwent clinical rating scales performed prospectively at baseline (within one month of surgery), and six months after STN DBS surgery with the stimulator on. Severity of PD was determined using the Unified Parkinson's Disease Rating Scale (UPDRS), Hoehn and Yahr staging score, Stand Walk Sit Test (SWST), and the Dyskinesia Rating Scale in both the off medication (PD medications held for 12 hours) and on medication state where appropriate.

The primary outcome measure was the change in UPDRS III off medication score at six months. Secondary outcomes included DBS stimulation parameters, adverse events, levodopa equivalent daily dose (LEDD), and DBS lead locations. The change in hemibody UPDRS III off motor scores were also calculated (summed unilateral UPDRS III score-items (20–26)) to correlate with the contralateral active electrode location.

Surgical methods and verification of lead location

The specifics of the surgical procedure have been published previously in greater detail [1]. All procedures were performed entirely within a 1.5T MRI scanner located in the Radiology department (Philips Intera, Best, The Netherlands). Patients were placed under general anesthesia and their heads were fixed in a carbon fiber head holder (Malcolm-Rand, CMI, San Clemente, CA) attached to the MRI gantry. A pair of flexible, receive-only loop MRI coils were positioned on either side of the head. The patients were initially placed in the scanner such that the top of the head was at the far end of the bore. This provided the surgical team with adequate access to the head for prepping, draping and opening. A specially designed surgical drape was used that adheres to the distal face of the scanner and the top of the patient's head, creating a flexible sterile field in the distal portion of the bore. Opening and burr hole placement were achieved using titanium instruments (KMedic, Teleflex Medical, Research Triangle Park, NC) and an MRI compatible pneumatic drill (Anspach, Palm Beach Gardens, FL). For this patient series, the Medtronic Nexframe MR (Medtronic, Minneapolis, MN) skull mounted aiming devices were used to implant the DBS electrodes. These devices were attached to the skull over the burr holes using self-tapping screws.

The patients were then moved to the isocenter of the scanner for targeting and implantation. A high resolution T2 slab acquisition through the region of the STN was obtained parallel to the commissures, and targets were selected in the posterolateral portion of the STN as visualized on a slice 4mm below the intercommissural plane. In the anterior-posterior dimension, the target was typically placed at the level of the anterior border of the red nucleus. In the medial-lateral dimension, the target was centered within the STN; if the lateral border of the STN was indistinct, more attention was paid to laterality from the midline and distance from the medial and posterior borders of the STN. The target was often initially placed at our default coordinates relative to the midcommissural point of X= 12mm, Y= −3mm and Z= −4mm and then modified as above based on visualization of the STN, with the goal of being at least 2mm from the medial, lateral and posterior borders of the nucleus. After alignment of the Nexframe MR on each side using rapid acquisition fluoroscopic MR sequences, ceramic stylets and peel-away sheaths were passed to the targets using serial imaging for confirmation of adequate placement. If adequate placement was not achieved, the stylets and sheaths were withdrawn and a second pass was performed.

The initial targeting accuracy was evaluated by determining the radial error of the first pass of the stylet; this was defined as the vector difference between intended and actual placement. Radial error was determined on the MR slice used for intraoperative target selection, 4mm below and parallel to the AC-PC plane.

After confirmation of adequate placement, the stylets were removed leaving the peel-away sheaths in the targets, and Medtronic model 3389 leads were placed down the sheaths with imaging obtained to confirm proper depth. The peel-away sheaths were then removed by pulling the proximal ends apart, which progressively withdrew the sheaths from the brain, leaving the DBS lead in place. The leads were anchored in standard fashion and their free ends tucked underneath the scalp for lead extension and IPG placement at a later date. All patients underwent postoperative volumetric T1 imaging immediately after skin closure for detailed lead location analysis. The coordinates of the active electrode(s) with respect to the midcommissural point were determined by obtaining the lead tip and entry coordinates in AC-PC space and calculating the center of each contact on the 3389 lead using proprietary software.

DBS Programming

Neurostimulator programming was initiated one to two weeks after implantation of the pulse generator. Each electrode was activated and tested separately in unipolar mode. Voltage-limiting adverse effects were noted. When improvements in PD symptoms were seen during programming sessions, patients were programmed chronically using the corresponding electrode(s). For patients in whom no clinical improvement was noted while programming, the electrode(s) within the dorsal STN was chosen for chronic stimulation. All patients were initially programmed using one electrode in unipolar mode, at 60 μsec pulse width and 130–145 Hz. The voltage was increased until adverse effects occurred and then reduced slightly. Patients returned for follow-up programming visits every one to two months.

Statistical analysis

Statistical analyses were performed in STATA 11 (StataCorp LP, College Station, Texas, USA). All baseline scores were compared to scores at 6-months using the non-parametric Wilcoxon matched-pairs signed-rank test for significance. The results were considered significant if $p < 0.05$.

Active electrode location at final follow-up was determined using the patient's postoperative MRI and calculating the point of stimulation in AC-PC coordinates relative to the midcommissural point. Using the generalized estimating equation (GEE) model we evaluated the influence of major covariates on percent change in contralateral hemibody UPDRS III score (items 20–26) at 6-months. This model was selected to control for possible within-patient correlations between brain hemispheres and body regions.

Standard Protocol Approvals, Registrations, and Patient Consents

The University of California, San Francisco Committee on Human Research (CHR, institutional review board) approved this study. All patients gave written informed consent after a detailed description of surgical options (including STN DBS implantation using standard stereotactic methods). The trial was registered with clinicaltrials.gov (National Clinical Trial number 00792532).

Results

Patient characteristics/Clinical Outcomes

Patient characteristics are summarized in Table 1. Seventeen advanced PD patients (9M/8F) were enrolled in this prospective study from 2007 – 2009. Mean age at time of surgery was 59.8 years and duration of PD was 11.1 years. Fourteen patients had follow up data available at 6 months. One patient developed a pulse generator infection that spread to the connector site requiring explantation of the entire system. Two other patients were lost to follow-up at six months.

The mean UPDRS III off medication score improved from 44.5 to 22.5 (49.44%) at 6 months ($p=0.001$) (Figure 1). There was a trend but not significant difference between baseline right body and left body scores ($p=0.07$), and no significant difference in the mean percent improvement of hemibody scores was evident at 6-months ($p=0.43$) (Table 2). UPDRS II, III on medication, and IV subscores also significantly improved ($p<0.01$) (Figure 1). Hoehn and Yahr scores in the off medications state improved after surgery (mean baseline 3.4 +/− 1.2 to 2.5 +/− 0.8 at 6 months (n=13 patients, $p=0<0.01$)). Dyskinesia Rating Scale score in the on medication state did not improve significantly after surgery (baseline 1.2 +/− 0.8 to 0.7 +/− 0.5 at 6 months (n=13 patients $p=0.16$)). SWST on the off medication condition showed improved performance in mean walking time ($p=0.03$) and number of steps ($p=0.02$) (n=11 patients). Patients who could not perform the SWST in less than 90 seconds were scored at a maximum score of 90 seconds and 90 steps (n=5 at baseline, n=1 patient at 6-months). LEDD decreased by an average of 24.7% ($p=0.003$). Average stimulation parameters were: 2.9V, 66.4μs, 154 Hz.

Initial targeting accuracy

Analysis of the initial stylet and peel-away sheath placement relative to the intended target was performed for all 17 patients enrolled in the study. The mean radial error of stylet placement after first pass was 0.8 ±0.4mm from intended target. Out of the 34 brain leads placed, 28 were placed with one stylet pass. Three lead placements required a second stylet penetration due to unsatisfactory trajectory to the intended target. Another three leads had satisfactory placement on the first pass but required a second pass down the same tract due to premature breakage of the peel away sheath during its removal.

Electrode location and clinical outcome

Relative to the midcommissual point, the average final lead tip location for all 17 patients (34 leads) enrolled in the study was X = 10.3mm, Y = −4.0mm, Z = −6.8mm. The mean active electrode location of the 14 patients included in the clinical outcomes analysis was X= −11.1mm, Y= −2.2, Z= −3.2mm in the left hemisphere and X= 11.8mm, Y= −1.5, Z= −3.3 in the right hemisphere (Table 3). GEE analysis revealed a significant influence of the Z-axis (the dorsal-ventral variable) predicting percent motoric improvement independent of the other covariates in our model (overall model $\chi^2= 14.37$, $p=0.013$; individual Z-axis β coefficient = −8.47, (95% CI: −15.60, −1.33) $p=0.02$). Age at time of surgery, duration of disease, X- axis, and Y- axis were not associated with percent improvement in UPDRS III hemibody score in our model.

Discussion

We describe the clinical outcomes of bilateral STN DBS in a series of 14 advanced Parkinson's disease patients all implanted with the interventional MRI technique. Overall the surgery was well tolerated. In the 17 patients that underwent surgery, the mean error of the initial stylet placement relative to the intended target was less than a millimeter (0.8mm).

After six months of chronic STN stimulation, patients experienced a mean improvement of 49.4% in the UPDRS III off medication score. The degree of improvement found in this study is comparable to the efficiency of STN in PD when leads are placed using traditional, frame-based, MER-guided stereotactic methods [21–27].

Previous studies of patients undergoing traditional DBS procedures have shown similar improvements in clinical outcome, with 41–59% improvement in UPDRS III, when comparing 6–12 month post-operative on stimulation/off medication to baseline off medication [21–24, 28, 29]. A review of 34 studies of bilateral STN DBS with a minimum of 10 patients and 6-month follow-up (between 1993 – 2004) revealed a mean 52% decreases UPDRS III scores after surgery in the stimulation-on and medication-off [30]. Our study, with a mean improvement of 49.44% improvement UPDRS III, follows this trend. In our previous publication detailing the technique and application of this surgical procedure, we reported retrospective outcomes in the original 14 patients implanted bilaterally by the iMRI technique. In that retrospective study, there was a slightly higher mean improvement of 60% (+/− 29%) in UPDRS III at a mean follow-up of 9 months [20]. This prospective study was specifically designed to address clinical outcomes after surgery [20].

Patients stimulated more ventrally throughout the STN territory had more improvement at 6-months after surgery. The underlying reason for this finding is not clear but may be explained by patients who tolerated activation of the deeper contacts without side effects had better located leads allowing for more improvement in hemibody scores. Historically, it has not been shown that stimulating in the more ventral area of the motor STN is move effective in treating parkinsonism. We cannot rule out the influence of a third unknown variable such as stimulation parameters, the influence of the volume and shape of stimulation, as well as the impact of axial symptoms not accounted for in the percent limb improvement. Improved methodology to define the active electrode location and stimulation volumes more precisely are needed to better correlate this variable with clinical outcome.

One potential advantage of this technique is the ability to place DBS electrodes in most cases with a single brain penetration, as opposed to traditional microelectrode guided procedures that involve multiple passes. In the current series, 28 of 34 electrodes were placed in one pass; the other 6 lead placements required a second pass. Three of these instances were due to stylet placement that appeared to be deviating from the intended trajectory; interestingly, two of these events happened in the same patient. The stylet and peel-away sheath were placed at a partial depth on both sides of the brain and imaging indicated that both stylets were heading slightly posterior to the intended trajectory. Both were removed and the Nexframe alignment was modified accordingly, with successful placement on a second pass on both sides. In the other three cases, a second pass was required due to premature breakage of the peel-away sheath during its removal after satisfactory lead placement. This was attributed to a technical issue with the peel-away sheath design that has subsequently been resolved. The targeting and first pass placement accuracy was acceptable in these three cases.

This case series has several limitations. A placebo response cannot be excluded, as patients and the neurologists rating the patients were not blinded to intervention (pre or post DBS) or medication status (on or off). Also, the follow-up time was limited to only 6 months. We are continuing to follow patients to understand long-term outcomes with this novel technique. This study also includes a relatively small number of patients and makes interpretation of lead location and outcome analysis challenging. Finally, the choice of whether to perform traditional awake surgery or iMRI-guided implantation was based on patient preference, or the recommendation of the surgical team for patients thought less likely to tolerate an awake

procedure. Because patients were not formally randomized to one technique versus the other, there may be some selection bias in the study population.

In this study we show that Parkinson's disease patients implanted using the iMRI method have comparable outcomes to those with frame-based microelectrode guided surgery. Many patients in the study expressed their desire to have DBS in a way that did not require them to be awake for the procedure or be off of their PD medications the day of surgery. This technique may be important for this subset of Parkinson's patients, as well as pediatric dystonia patients and anyone undergoing DBS where awake surgery may not be a realistic option. It may also have other advantages including shorter operative times and fewer brain penetrations than most traditional methods of DBS surgery.

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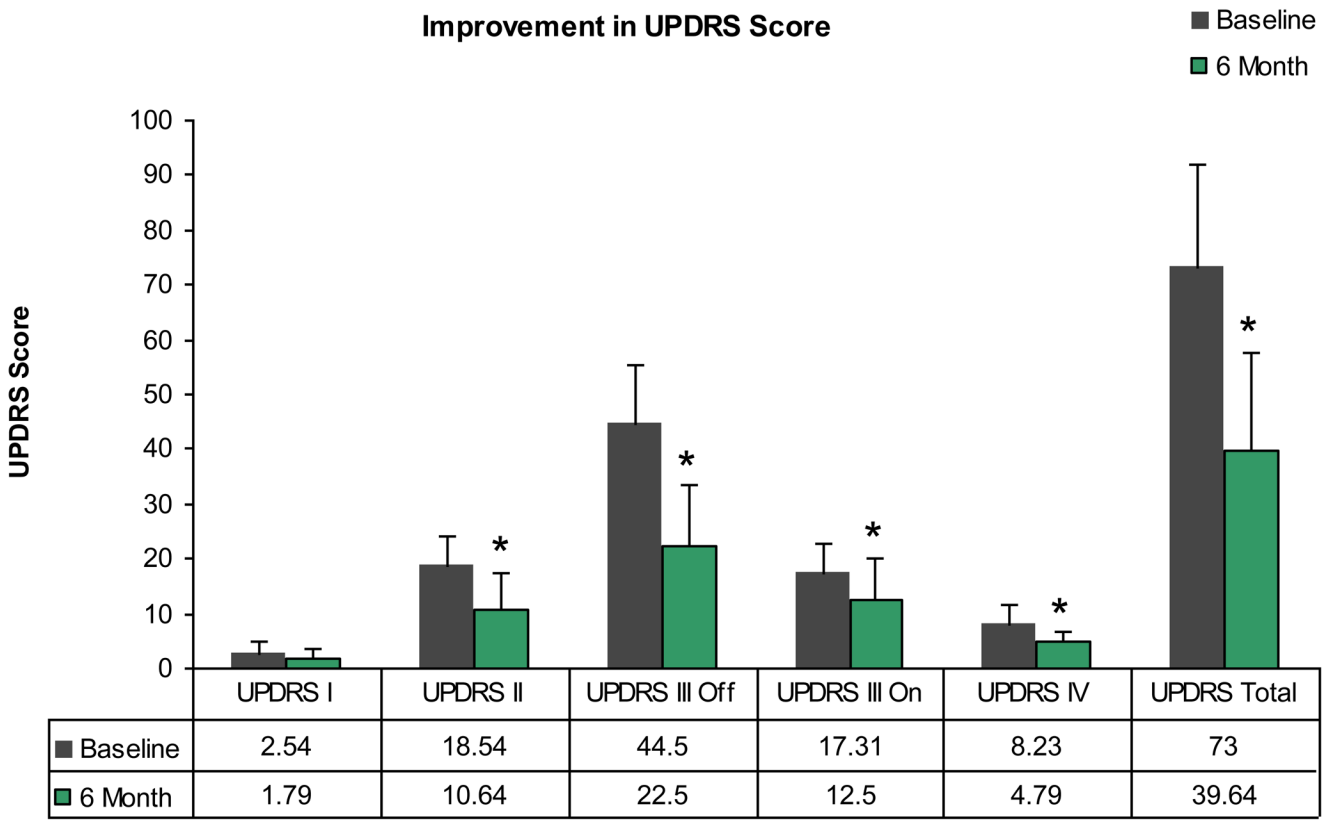

	UPDRS I	UPDRS II	UPDRS III Off	UPDRS III On	UPDRS IV	UPDRS Total
Baseline	2.54	18.54	44.5	17.31	8.23	73
6 Month	1.79	10.64	22.5	12.5	4.79	39.64

Figure 1. Results of iMRI STN DBS on UPDRS Scores (n=14)

UPDRS – Unified Parkinson's Disease Rating Scale raw score on X-axis. The Wilcoxon signed-rank test was significant compared to baseline for UPDRS II, III on medications, and IV ($p<0.01$), and for UPDRS III off medications ($p=0.001$). * indicates significant difference at $p<0.05$.

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Table 1

Baseline Patient Characteristics

LEDD – Levodopa equivalent daily dose (mg) a dose of 100 mg of levodopa is equal to 125 mg of controlled-release levodopa is equal to 10 mg of bromocriptine is equal to 1 mg of pergolide is equal to 4 mg of ropinrirole is equal to 100 mg of amantadine is equal to 333 mg of comtan, is equal to 1 mg pramipexole is equal to 80 mg of stalevo. [31]

Patient	Age (yrs)	Sex	Duration of PD (yrs)	UPDRS III off	UPDRS III on	% Change UPDRS	UPDRS Total	Hoehn Yahr off	LEDD (mg)
1*	66	F	15	40	9	77.50	63	3.0	1258
2	58	M	12	60	18	70.00	97	3.0	1750
3	50	M	8	32	12	62.50	48	2.0	1090
4	57	M	6	37	16	56.76	56	5.0	2394
5	64	F	12	55	NA	NA	NA	3.0	1002
6**	59	M	15	44	22	50.00	81	3.0	1140
7**	58	M	8	46	6	86.96	94	4.0	1560
8	62	F	11	54	13	75.93	94	5.0	862
9	66	M	12	44	21	52.27	77	3.0	1516
10	62	F	7	34	23	32.35	69	4.0	340
11	60	M	15	41	25	39.02	66	2.0	1376
12	54	M	7	27	11	59.26	45	2.0	2065
13	56	F	8	54	9	83.33	97	4.0	1354
14	57	F	9	58	25	56.90	89	4.0	1380
15	65	F	10	31	13	58.06	52	2.0	825
16	67	F	24	50	16	68.00	89	5.0	1180
17	55	M	9	46	23	50.00	70	3.0	1635
Mean (+/−SD)	59.8 (4.8)	9M/8F	11.1 (4.4)	43.3 (11.2)	15.9 (7.4)	60.2 (19.8)	71.4 (20.3)	3.4 (1.1)	1337 (482)

*Excluded from the analysis (patient explanted at month 2)

**Follow-up data missing

Table 2
Mean UPDRS III Off Medication Hemibody Scores

UPDRS III scores at baseline and at 6-months (on stimulation) calculated from summed unilateral UPDRS III score-items (20–26).

Hemibody Score	Baseline Mean (SD)	6 Month Mean (SD)	Mean % Change
Left	15.6 (4.1)	7.3 (4.7)	53.8%
Right	13.4 (4.8)	7.1 (4.6)	46.1%
Left vs. Right	p=0.07	p=0.97	p=0.43

Table 3

Mean active electrode location

Mean Active electrode location relative to the midcommissural point (mm) determined from postoperative MRI (N=14 patients)

Brain Hemisphere	X	Y	Z
Left	−11.1	−2.2	−3.2
Right	11.8	−1.5	−3.3