Initial Results of Bilateral Subthalamic Nucleus Stimulation for Parkinson Disease in a Newly Established Center in a Developing Country: Shiraz, Southern Iran

Ali Razmkon[1], Omid Yousefi[1], Raziyeh Rezaei[1], Sina Salehi[2], Peyman Petramfar[3], Arash Mani[4], Hashem Rahmati[5], Janardan Vaidyanathan[6], Ghazal Ilami[1], Yalda Amirmoezzi[1]

OBJECTIVE: **To report the establishment of a new center for deep brain stimulation (DBS) as a surgical treatment for Parkinson disease and the surgical outcomes, from 2014 to 2017 in Shiraz, Southern Iran.**

METHODS: **A new treatment program was established in Shiraz through a multidisciplinary team in 2014. Thirty-four patients underwent implantation of subthalamic nucleus (STN) electrodes during the last 3 years. Twenty-five patients fulfilled the minimum 6-month follow-up criteria. The baseline Unified Parkinson Disease Rating Scale (UPDRS) was assessed 1 month before surgery in both off-medication and on-medication states by a movement disorder neurologist. To evaluate the outcomes, subscores of the UPDRS were assessed in all patients before surgery and at least 6 months after the operation.**

RESULTS: **All 25 patients had advanced Parkinson disease categorized as stage 3 or 4 using the Hoehn and Yahr scale. STN DBS resulted in a dramatic improvement in motor function of most patients. A reduction in dopaminergic medication dosage (average 60% reduction) was observed. The mean improvement was 40% in UPDRS II and 67% in UPDRS III. No surgical or hardware complications were observed. Stimulation-related adverse effects, including increased falling and worsening of speech, occurred in a few patients after surgery. Most of the patients experienced weight gain after surgery.**

CONCLUSIONS: **Bilateral STN DBS is a satisfactory and safe treatment for carefully selected patients with advanced Parkinson disease. According to the results, the procedure can be performed safely and with comparable results in developing countries around the world.**

INTRODUCTION

Deep brain stimulation (DBS) is an effective therapy for Parkinson disease, tremor, dystonia, and other complex neurologic and psychiatric disorders. This therapy has been used since 1990 in many centers across the world.[1] Although expensive and technically demanding, DBS is performed frequently, and numerous publications have documented its safety, benefits, and adverse events.[2-5] According to the current literature, the mean improvement in Unified Parkinson Disease Rating Scale (UPDRS) III is reported to be between 28% and 71% after surgery.[6-9] The surgery also results in 19–72% medication reduction among patients.[10-12] Although DBS is expensive, strong pharmacoeconomic studies show that, in the long term, it reduces the cost of care in surgically treated patients.[13]

The population of Iran (approximately 80 million people) is aging rapidly. More than 6% of the population is older than 60 years, which is estimated to rise steeply to 10.5% by 2025.[14] This fact increases the likelihood of acquiring neurodegenerative diseases, such as Parkinson disease, leading to increased disease burden and costs. Population-based, door-to-door studies have shown the prevalence of Parkinson disease to be as high as 285 per 100,000 population in Iran, which is considered a medium-to-high rate.[14,15] This prevalence necessitates the need to introduce new treatment modalities that will reduce disease burden. Shiraz is a major city in southwest Iran and is the referral medical center for the southern half of the country, covering at least 25 million

Key words
- Deep brain stimulation
- Developing country
- Parkinson disease
- Subthalamic nucleus

Abbreviations and Acronyms
DBS: Deep brain stimulation
INS: Implantable neurostimulator
MRI: Magnetic resonance imaging
STN: Subthalamic nucleus
UPDRS: Unified Parkinson Disease Rating Scale

From the [1]Research Center for Neuromodulation and Pain, Kowsar Hospital, Shiraz; [2]Shiraz Neuroscience Research Center, [3]Department of Neurology, [4]Research Center for Psychiatry and Behavioral Sciences, and [5]Community-based Psychiatric Care Research Center, Shiraz University of Medical Sciences, Shiraz, Iran; and [6]Medtronic, Mumbai, India

To whom correspondence should be addressed: Ali Razmkon, M.D. [E-mail: ali.razmkon@gmail.com]

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inhabitants. Establishment of a new center for DBS surgery was crucial and economically beneficial for the population.

We established the DBS surgical program in Shiraz in 2014. Trade sanctions made the journey challenging by limiting the availability of products. We did our best to ensure patient safety and achieve optimal outcomes. Multidisciplinary team work was ensured to guarantee perfect results. In this retrospective case series, we report the outcome of our first series of patients who underwent DBS as surgical treatment for Parkinson disease.

METHODS

Strategies to Establish a New Center

After defining the disease burden and estimating the number of patients with Parkinson disease in our referral population, we developed a multidisciplinary team comprising a stereotactic and functional neurosurgeon, movement disorder neurologist, neurophysiologist, psychologist, and social worker, in addition to trained surgical technicians, radiographers, and nurses. This team could access a radiologist, a nuclear medicine specialist, and a physicist for technical support of the imaging issues. Sufficient training was obtained both internationally for the specialists and locally for other members of the team. We received support from a visiting movement disorder neurologist and an industry procedure solutions expert during the first cases to ensure patient safety and optimal outcomes.

Logistical Issues

Different issues included gaining access to proper operating rooms for elective procedures, organizing multidisciplinary patient clinics, access to modern magnetic resonance imaging (MRI) scanners, stereotactic equipment with necessary software and procedure reimbursement. Patients could benefit partially from government support for the device, as well as basic and complementary insurances to facilitate this surgery. Scientific seminars were held to create awareness among neurologists regarding this therapy and to facilitate patient referral for screening by the multidisciplinary team.

For the first 2 patients, stereotactic MRI sequences were obtained, and no fusion was used, However, for later patients, we acquired nonstereotactic (i.e., without a frame), target-specific, high-resolution MRI sequences before surgery and fused then with stereotactic computed tomographic scans obtained on the day of surgery. A Leksell G stereotactic frame (Elekta, Stockholm, Sweden) with a Framelink planning workstation (version 5.4.1; Medtronic, Minneapolis, Minnesota, USA) and Leadpoint 4 (Medtronic) intraoperative electrophysiology monitoring system were used in the latter cases. For the initial 2 cases, planning was performed using Stereonauta software (Estudios e Investigaciones Neurológicas, Madrid, Spain) and intraoperative electrophysiology using a Neurostar system (Neurostar, Tübingen, Germany). The idea of using nonstereotactic MRI empowered us to use a plan-ahead paradigm and thus decouple imaging and planning from the day of surgery. The targets and respective trajectories were planned with respect to the midcommissural point and were expressed in functional coordinates. Fusion with the stereotactic CT transformed these functional coordinates to stereotactic coordinates.

Patient Selection

To provide optimal care for patients with Parkinson disease, all patients with movement disorders (e.g., Parkinson disease, dystonia, tremor) were referred to the movement disorder clinic. Only patients with severe Parkinson disease were enrolled in this retrospective case series. Eligible patients selected by the movement disorder neurologist were referred to a panel commission held monthly by all the members of the team. DBS candidates were selected by the consensus among the whole team based on the following criteria: clinically proven advanced idiopathic Parkinson disease (at least stage 3 on the Hoehn and Yahr scale), good response to levodopa (a positive inpatient levodopa challenge test), severe levodopa-induced dyskinesias, and the absence of any other comorbidities, surgical contraindications, or proven cognitive or psychiatric problems, such as severe depression or psychosis. An acceptable response in levodopa challenge test was defined as an at least 30% improvement in Unified Parkinson's Disease Rating Scale (UPDRS) part III scores after drug administration. All patients underwent a thorough neuropsychologic assessment by the psychologist to exclude ones with cognitive or psychiatric impairment. All patients with severe cognitive impairment, such as dementia and diagnosed psychiatric disorders, were excluded.

The baseline scores of UPDRS III were measured for off- and on-medication statuses by the movement disorder neurologist for every patient 1 month before the operation. Patient characteristics are presented in **Table 1**.

Preoperative Planning

All selected patients with Parkinson disease underwent preoperative nonstereotactic (i.e., without a frame) high-resolution MRI using target-specific sequences (1.5-T; MAGNETOM-Avanto; Siemens Healthcare, Erlangen, Germany) 1–2 days before the operation. A vitamin E capsule was placed adjacent to the ear lobe on the right side as a marker, allowing us to differentiate left and right sides on nonstereotactic images. The MRI laser marker was aligned to ensure that the Ried baseline (a line joining the inferior margin of the orbit to the center of the external auditory meatus) was parallel. The anesthesiologist ensured airway access and sedation to ensure that images were without any movement artifact. Total acquisition time for all sequences was approximately 25 minutes per patient. The following target-specific neuronavigation compatible sequences were obtained:

1. Multiplane reformattable axially acquired, T1-weighted isotropic (1 × 1 × 1 mm) voxel sequences from the hard pallet to vertex with and without contrast (acquired as the last sequence)
2. Two-millimeter T2-weighted axial sequences in the region around the anterior commissure - posterior commissure plane (15 slices above and 15 slices below)
3. Two-millimeter T2 weighted coronal sequences centered at the midcommissural point (15 slices anterior and 15 slices posterior)

Preoperative functional planning of the bilateral subthalamic nucleus (STN) target and trajectories was performed with a safety

Table 1. Characteristics of Patients Enrolled in the Study

Patient Number	Age (Years)	Sex	Duration of Disease (Years)	Preoperative LDED (mg)	Postoperative LDED (mg)
1	53	Male	12	1500	1500
2	45	Male	12	1500	375
3	39	Male	3	625	750
4	48	Male	11	1500	750
5	46	Male	5	1250	375
6	36	Female	13	875	125
7	62	Male	12	2000	875
8	64	Female	16	1000	250
9	52	Male	9	2000	1250
10	45	Male	8	5000	375
11	53	Female	13	3000	0
12	57	Female	11	750	750
13	15	Male	3	1125	1125
14	41	Female	15	2500	1000
15	71	Male	15	1000	750
16	48	Female	15	1500	1500
17	62	Male	20	1000	375
18	63	Male	18	2000	1000
19	55	Female	13	2500	250
20	61	Female	13	3000	375
21	49	Male	8	1000	750
22	49	Male	8	3000	500
23	70	Male	14	1250	1000
24	54	Male	13	800	375
25	59	Male	10	750	500
Mean ± SD	51.9 ± 11.9		11.6 ± 4.2	1697.0 ± 1016.9	675.0 ± 408.2

LDED, levodopa daily equivalent dose.

margin for performing microelectrode recording. The STN was visualized on the axial and coronal T2-weighted images using principles of direct visualization, and it was thereafter compared with standard atlas indirect visualization coordinates. The locations of the individual electrodes in the planned trajectory were confirmed to ensure maximum traversal of the STN. A 10-mm look ahead was performed to ensure that no vital structures were encountered beyond the target.

Surgery

On the morning of surgery, the stereotactic frame was fixed to the patient's head under long-acting local anesthetic. The patient underwent a stereotactic computed tomographic scan (Brilliance iCT; Philips Healthcare, Cleveland, Ohio, USA) and transferred to the operating room. After fusion of the stereotactic computed tomographic image to the nonstereotactic MRI on the planning software, the stereotactic frame coordinates were obtained.

The surgery was performed under conscious sedation using continuous infusion of dexmedetomidine and propofol. Only in one 15-year-old patient received general anesthesia. The surgery was performed using microelectrode recording to identify the boundaries of the target, followed by macroelectrode stimulation.

For microelectrode recording of STN activity, we usually inserted 3–5 parallel tungsten microelectrodes (FHC Inc., Bowdoin, Maine, USA) through Ben gun and advanced the electrodes using a microdrive with 0.5- or 1-mm increments, starting from 10 mm above until a few millimeters below the target. In each depth, the multiunit activity from all electrodes were observed and retrospectively saved in the 10-second period. The data were filtered with a 300–5000-Hz band-pass filter, sampled at a rate of 48 kHz, converted to digital, and stored in a computer for inspection and

Table 2. Mean UPDRS Subscores and Improvements in Patients

Measures	Preoperative	Postoperative	Improvement (%)	*P* Value
UPDRS II	19.88 ± 5.80	10.58 ± 7.59	46%	0.002
Falling	1.11 ± 1.16	1.05 ± 1.39	5%	0.892
UPDRS III	42.52 ± 12.67	14.41 ± 12.52	66%	0.001
Tremor	10.58 ± 4.91	3.47 ± 4.43	67%	0.006
Rigidity	8.11 ± 3.14	1.7 ± 3.15	79%	<0.0001
Bradykinesia	2.05 ± 0.42	0.88 ± 0.69	57%	0.01
Speech	1.29 ± 0.84	1.0 ± 0.86	22%	0.260
Finger taps	3.05 ± 1.14	0.94 ± 1.08	68%	0.001
Hand movements	3.05 ± 1.08	0.64 ± 0.86	79%	0.001
Rapid alternating movements	3.23 ± 1.25	0.88 ± 0.99	72%	0.001
Leg agility	3.35 ± 1.22	0.76 ± 1.03	77%	0.001
Gait	1.76 ± 0.66	0.82 ± 0.88	53%	0.05
Arising from chair	1.70 ± 0.91	0.76 ± 0.66	55%	0.004
Postural stability	1.70 ± 0.68	1.05 ± 0.65	38%	0.013
Levodopa daily equivalent dose	1697.0 ± 1016.9	675.0 ± 408.2	60%	0.001

UPDRS, Unified Parkinson Disease Rating Scale.

analysis using a Leadpoint system (Medtronic, Skovlundae, Denmark, and Shoreview, Minnesota, USA). After each recording session, we evaluated the stored data from all depths and electrodes to select the best trajectory for permanent lead implantation. The best trajectory was selected by visual inspection of the data, ensuring the maximal length of STN activity. The STN activity was identified by considering different features of the signal such as amplitude of background activity and pattern of neural firing.

When the best trajectory was selected, the microelectrode cores of the electrode were withdrawn, and intraoperative macrostimulation was performed through the outer part to ensure acceptable clinical response in that trajectory. Along the selected trajectory path, 3–5 depths with 15–20 mm of distance were considered for macrostimulation. In each depth, we performed the electrical stimulation using a 1–5-mA constant current (with 1-mA increments) biphasic pulse, at 130 Hz and with a 60-μs pulse width while the neurologist evaluated the patient's motor symptoms (rigidity, tremor, and bradykinesia) and the presence of any adverse effects. The neurologist assessed effects and adverse effects to qualify the selected trajectory for final lead implantation. Common adverse effects included any abnormal muscular contraction at the extremities and face, eye deviation, pupillary change, abnormal sensory complaints, and speech disturbance.

The permanent lead (model number 3389; Medtronic) trajectory and position was verified with intraoperative lateral fluoroscopy. Postoperatively, stereotactic computed tomography was used to audit lead location. Deviation of less than 1.5 mm from the planned target was considered acceptable. One of the leads required repositioning in 2 patients.

The implantable neurostimulator (INS; model number 37601, Activa PC; Medtronic) was implanted in all but 1 patient for whom we implanted a rechargeable device (model number 37612, Activa RC; Medtronic) in the right subclavicular area on the same day or the day after.

Postoperative Course

All patients received maintenance short-acting levodopa medication early after the operations. They were mobilized on the following day and discharged 2 days later from the hospital. Initial programming of the device was done at least 2 weeks after the surgery to allow for resolution of the micro-subthalamotomy effect.

Outcome Parameters

UPDRS score and subscores before and at least 6 months after the surgery were recorded for every patient. Medication dosage and daily diaries, including on and off phases, were also recorded. Data were analyzed using SPSS software version 20. Wilcoxon test was used to compare serially recorded outcome data.

RESULTS

Bilateral STN DBS was performed on 25 patients with Parkinson disease (68% were male and 32% female) with a mean age of 51.9 ± 11.9 years. One 15-year-old patient did not skew the mean significantly as an outlier. All the patients were levodopa dependent for daily routine activities, and the mean levodopa dose equivalent was 1697 mg. Because of the high dose of dopaminergic requirement, 83% of the patients experienced severe dyskinesia for

an average duration of 50% of the time. Tremor score in UPDRS III, at least 6 months after surgery, changed from 10.5 ± 4.9 on an average to 3.4 ± 4.4 (67% improvement). Rigidity and bradykinesia improved by 79% and 53%, respectively. Improvements in gait and postural stability as are shown in **Table 2**.

STN DBS resulted in a reduction of levodopa equivalent daily dose by 60%. Consequently daily off-times were reduced from 6–8 hours to an average of 3 hours/day according to patient diaries. The average improvement in UPDRS II was 40%.

No surgery- or hardware-related complications (e.g., hemorrhage, cerebrospinal fluid leakage, ischemic events) happened in our series. Only 2 patients experienced postoperative transient confusion for 2–3 days. We observed a few documented stimulation-induced adverse events. In 3 patients, the rate of falls increased early after the surgery, but after adjusting the INS, they had less difficulty in walking and fewer falls. Worsening of speech also happened in 3 patients. Twenty-two patients had weight gain after surgery, but remained in the normal range for body mass index.

DISCUSSION

Parkinson disease is an extrapyramidal movement disorder characterized by symptoms of tremor, rigidity, and bradykinesia.[16] At the onset of the disease, symptoms can respond to low doses of levodopa, but as the disease progresses, patients need higher doses of levodopa to alleviate their symptoms; this can result in severe dyskinesias. In such cases, surgical intervention can relieve symptoms. STN is considered more preferable than the globus pallidus interna for alleviating off-phase motor symptoms.[17-19]

STN DBS causes improvement in many aspects of UPDRS, although some subscores are affected less than the others. UPDRS I, which reflects cognitive and behavioral issues, is hardly affected after surgery. In addition, many cognitive and psychiatric complications can be expected after STN DBS. Increases in suicidal ideation, attempted suicide, depression, and confusion are some of the complications.[20,21] We only observed postoperative transient confusion for 2–3 days in 2 patients, which has been reported elsewhere.[4]

Postural instability, gait disturbance, and speech disorders, which are the non–dopamine-dependent symptoms of Parkinson disease, might not respond to bilateral STN DBS. Three patients in our series experienced difficulty with axial balance and reported more frequent falls compared with their preoperative status. We could achieve improvements in balance with INS reprogramming as has been reported in similar studies.[22]

The main goal of STN DBS is to improve the motor function of patients, and this is evaluated with UPDRS part III. We achieved a 66% mean improvement in UPDRS III scores. Speech might worsen after surgery. Postoperative hypophonia can be a result of the reduction in levodopa equivalent daily dose.[2,23,24] We observed speech issues and significant hypophonia in three patients, which did not respond well to further programming.

A 19%-72% reduction in levodopa equivalent daily dose has been reported to occur after surgery in different studies, and subsequently, patients experience dyskinesia for shorter periods of time and with less severity.[7,9,10,12] A 60% reduction in mean levodopa equivalent daily dose is comparable to other studies.[7,9,10,12] One of the most important predictors of motor outcome is patient response to the levodopa challenge test before the procedure.[25] Our patients had 47.5% improvement in UPDRS III scores after administering the levodopa challenge test.

Device-related adverse events, including hardware failure, lead migration, and infection, can occur in STN DBS.[2] Hemorrhage has been reported in almost 5% of patients.[5,26-29] We did not observe any of these surgery- and device-related complications in our current series. Only 2 patients experienced postoperative transient confusion for 2–3 days. Twenty-two of 25 patients had weight gain after STN DBS, which has been reported in other studies.[30-32]

Local Issues

The unique aspect of this report includes the challenges and experiences occurring during the preliminary phases of establishing this technique in a developing country. In the following sections, we briefly describe different issues encountered during our experience.

Support from Different Resources. Obtaining hospital and governmental support for performing such a complex surgery for the first time was challenging. As stated earlier, we started to hold subspecialty seminars in the region with the permission of hospital, university, and ministry authorities. We aimed to present the outstanding outcomes associated with movement disorder surgery, which could easily be presented in an objective way (e.g., showing video clips of treated patients before and after surgery). Alternatively, we focused on the cost-effectiveness of this therapy considering the significant reduction of patient's medication and return to work. After several months of challenge, these seminars could convince the authorities for providing support in preparing the hardware and allocating resources. The seminars and lectures did not stop after starting the experience; therefore, we aimed to present the initial outcome of every case in different joint conferences to attract the attention of authorities and referring physicians.

By contacting the manufacturing company (Medtronic), we could also facilitate the device procurement through registered local agents. The company also supported the presence of an international visiting movement disorder neurologist for patient selection in initial cases and an industry procedure solutions expert during the first set of procedures.

Patient Referrals. Initially, there were strong misconceptions about the safety, feasibility, and affordability of the procedure among the neurologist community. Joint seminars and conferences were unable at the beginning to attract the attention and interest of neurologists. We established our team with the presence of the only 2 movement disorder neurologists in our region, and we received the support of an international visiting neurologist for patient selection in initial cases. In addition to the joint conferences, social media resulted in a many referrals to our clinic from all over the country. As the number of cases increased, we observed a growing interest among the neurologist community. Currently, about approximately 100 Iranian patients are referred monthly to our center from all across the country, of whom 4–5 eligible patients are scheduled every month.

Economical Issues. More than 90% of the Iranian population benefits from baseline governmental insurance plans including social security organization, medical service insurance organization, and the military personnel insurance organization. This governmental insurance covers up to 70% of costs of certain drugs and 90% of public hospital expenses. A number of semipublic and private insurance programs are also available as complementary voluntary insurances, which cover extra costs relevant to private or semipublic hospitals.[33]

The cost of the DBS hardware remains the biggest expense of DBS surgery in our country, whereas hospital costs comprise less than 30% of the whole expense. The DBS device is a high-cost product; therefore, its direct procurement is costly to patients and the health system. After long conversations and convincing the health ministry authorities of the cost-effectiveness of DBS therapy for patients with movement disorders, the ministry allowed the importation of the device through the Heyat Omana Arzi (HOA; the Board of Trustees for Patient Treatment with international currency saving). HOA is a nongovernmental organization related to the ministry of health; it imports the necessary high-cost healthcare devices using reasonable currency equivalence in a tax-exempt way. This process decreases the cost of the device of approximately $20,000 US to almost half, after which the basic and complimentary insurance cover 70%–100% percent of the cost.

We performed our first 8 cases in a public setting with full governmental support, and the patients paid approximately 10% of the expenses. Afterwards, because of the inability of the hospital to pay for the high cost of the device and improper infrastructure, we had to switch to a semipublic charity-based center (Shiraz Kowsar Hospital). Currently, the patients with most basic insurance have to pay approximately $3000 US for the device, and approximately $3000 US for hospital costs. A separate team evaluates patient ability to pay the expenses, and may introduce them to the hospital charity system for further economic support in certain cases. Patients with better insurance coverage pay fractions or none of the costs. Although we try our best to reduce the final payment as much as we can, it seems that only the middle and higher socioeconomic class of the society can benefit from this therapy. Because of the lack of sufficient experience with ablation techniques and the unavailability of hardware, we could not provide such treatment for eligible cases including those who were unable to pay for the costs in this stage.

CONCLUSION

Bilateral STN DBS resulted in a dramatic effect on motor functions in all patients during the follow-up period. In addition, there was significant reduction in levodopa equivalent daily dose in most patients. Further study is required over the following years to evaluate the long-term effects of STN DBS at our center. In our experience, ensuring a multidisciplinary team approach, adequate clinical training and efficient logistics are necessary prerequisites to ensure that the procedure can be performed safely with comparable results in developing areas around the world.

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