Subthalamic Deep Brain Stimulation in Parkinson's Disease: A Boon or Bane – A Single Centre Retrospective Observational Study from India

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Abstract

Background Subthalamic deep brain stimulation (STN-DBS) for refractory Parkinson's disease (PD) is more of a modality of treatment that is empirical, for which a physiological explanation is being sought. This study was done to determine the outcome and complications of patients undergoing STN-DBS for PD.

Methods This retrospective observational cohort study was conducted in an advanced neuromedicine facility in eastern India for 9 years (August 2013–August 2022), which included all patients undergoing STN-DBS.

Results A total of 53 patients were operated on during the study period. The mean age group of the study population was 60.5 (standard deviation [SD]: 8.2) years with a male (33 [62.3%]) predominance. The most common presenting complaints included rigidity and hypokinesia (27), severe dyskinesia (21), and tremors (17). During the postoperative period, rigidity and hypokinesia (21), severe dyskinesia (16), and tremors (12) improved significantly in a subset of the patients. The majority (45 [84.9%]) of these cases received bilateral monopolar simulation, whereas three patients (5.7%) had bilateral bipolar stimulation. Unilateral bipolar stimulation was used in five (9.4%) patients. In the immediate postoperative period, they were initiated on limb, speech, and swallowing therapy as indicated. Surgery-related complications were seen in five (9.4%) cases. At 6 months of follow-up, a significant improvement in the Unified PD rating scale component (mainly motor examination and complication of PD therapy) was noted in the majority (36 [67.9%]) of patients. One patient developed neuroleptic malignant syndrome and succumbed to his illness on the fourth postoperative day.

Conclusion Given these findings, STN-DBS appears to be a good, safe, and effective treatment for a subset of medically refractory PD with an overall improvement in two-thirds of the study cohort and less than 10% risk of complications.

Keywords
► Parkinson's disease
► deep brain stimulation
► subthalamic deep brain stimulation
► movement disorder

Introduction

Parkinson's disease (PD) is one of the most prevalent neuro-degenerative disorders in India and abroad.[1] A recent systemic review and meta-analysis from 1980 to 2019 in the Indian population showed the prevalence of PD to be 0.8 per 1,000 population (95% confidence interval [CI]: 0.4–1.3; $p < 0.01$; $I^2 = 95\%$).[2] Tremor, rigidity, bradykinesia, and postural instability are the most common clinical manifestations of PD. Approximately 75% of these patients have a resting tremor, which is the disease's defining symptom.[1,3] The illness progresses gradually with a prevalence of about 0.3% in the general population, making it the most prevalent movement disorder in middle or later life.[4] At the molecular level, the lack of dopamine at the nigrostriatal terminals in the basal ganglia causes signs and symptoms of PD.[3,5] However, from a neurophysiological perspective, it appears that the motor symptoms of PD are primarily caused by abnormalities in one of the numerous parallel and largely segregated basal ganglia thalamocortical circuits in the human brain.[6,7] The thalamus, cortex, and brainstem's downstream network may be disrupted when one or more of these circuits are dysfunctional alone or together.[6,7]

Over the years, several treatment options have been created to address the motor complications of PD, which have a significant impact on quality of life and psychosocial well-being. Dopaminergic agonists and then levodopa (L-dopa) were introduced, which quickly became the mainstay of treatment.[8] However, the restrictions and drawbacks of levodopa therapy for PD have been extensively documented in the literature.[8–10] Many patients experience medication-related motor complications 5 years after initiation of treatment, in the form of levodopa-induced dyskinesias (LID) and motor fluctuations.[3,8] There is little in the way of medical management for motor complications in patients with advanced PD, so surgical interventions are used as a treatment in refractory cases.

The primary objective of surgical treatment for PD is to improve motor control. Surgery should be opted for considering a patient's symptoms, age, functional disability level, comorbid conditions, preference, and the likelihood of overall benefit. In recent times, deep brain stimulation (DBS) is proven to be beneficial for the medically intractable treatment of PD. Both subthalamic nucleus (STN) and globus pallidus internus (GPI) stimulation are efficient in reducing dyskinesias and ameliorating PD symptoms.[7,11,12] As per a recent hypothesis, DBS works by sending an electrical current that can be modulated to a particular target region of the brain by altering the voltage, frequency, and duration of each electrical pulse that is delivered. Depending on the parameters used for stimulation, the energy that is delivered generates an electrical field that can vary and be controlled externally. Although the whole procedure was originally thought to stimulate the target, hence the name, it appears that DBS excites the neuronal fibers but inhibits the neural cells. However, it is still unclear exactly how DBS alters the rate and pattern of neuronal firing and how these modifications alter PD symptoms.[7,11,12] DBS is currently more of an empirical supportive therapy, for which a physiological explanation is being sought. This retrospective observational cohort study from India was done to determine the outcome and complications of patients undergoing STN-DBS for PD.

Methods

Study Design and Setting

This retrospective observational cohort study was conducted in an advanced neuromedicine facility in eastern India for 9 years (August 2013–August 2022). This facility has 195 beds (including an intensive care unit and general ward beds) and accommodates both neurosurgical and medical patients.

Participants and Selection Method

All the patients undergoing bilateral subthalamic nucleus deep brain stimulation (STN-DBS) during the study period were included in the study. A careful preoperative selection of patients is necessary to identify those who will respond to and tolerate the therapy to get the most benefit. A 10-point criteria chart was prepared, of which the following 8 points had to be a "yes"[13]: age less than 75 years, idiopathic PD (i.e., no progressive supranuclear palsy/multiple system atrophy/corticobasal degeneration/Lewy body dementia), levodopa responsive, poor/adverse response to the drug (increased off period, disabling dyskinesia, disabling motor fluctuations), degree of disability unified PD rating scale (UPDRS) part III score greater than 25, neuropsychology Mini-Mental State Examination (MMSE) greater than 24, levodopa challenge response positive (30% improvement in UPDRS after 12 hours off medication), and willing for surgery and programming. Patients not requiring long-term anticoagulation and advanced comorbidities were excluded after a detailed medical/neurological examination and judging the risk–benefit from the said surgery (►**Table 1**).[13] Clinical outcomes based on UPDRS at 6 months were evenly coded and/or analyzed.

Anesthetic Considerations

Each patient had a thorough clinical and laboratory preoperative evaluation, and the following parameters were considered intraoperatively: normotension, normocarbia or slightly elevated EtCO$_2$, and normothermia to mild hypothermia. Patients with severe tremors and restlessness were operated on under general anesthesia (GA), while the rest underwent awake surgery under scalp block and local anesthesia infiltration for the burr hole.

Radiological Imaging

DBS magnetic resonance imaging (MRI) was done before the day of surgery, while for patients with severe tremors and restlessness imaging was done just before surgery after induction of GA. The DBS MRI protocol includes T2-weighted images for STN targeting (repetition time [TR]: 2,800 milliseconds; echo time [TE]: 90 milliseconds; flip angle: 90 degrees; and slice thickness: 2.0 mm); followed by magnetization prepared rapid acquisition gradient echo (MPRAGE) sequences (slab thickness: 240 mm; effective

Table 1 Preoperative 10-point selection criteria chart to undergo subthalamic deep brain stimulus (STN-DBS) for refractory Parkinson's disease[13]

Sl. no.	Variables of selection criteria chart	Responses
1.	Age less than 75 y	Yes/no
2.	Idiopathic Parkinson's disease (i.e., no progressive supranuclear palsy/multiple system atrophy/corticobasal degeneration/Lewy body dementia)	Yes/no
3.	Responsive to levodopa	Yes/no
4.	**Levodopa related**	
	i. Poor or adverse effect	Yes/no
	ii. Increased off-period	Yes/no
	iii. Disabling motor fluctuations	Yes/no
	iv. Disabling dyskinesia	Yes/no
5.	Degree of disability: unified Parkinson's disease rating scale part III score > 25	Yes/no
6.	Neuropsychology: Mini-Mental State Examination > 24	Yes/no
7.	**Levodopa challenge**	
	i. Positive response to levodopa challenge	Yes/no
	ii. 30% improvement in unified Parkinson's disease rating scale after 12 h off medication	Yes/no
8.	Advanced coexisting medical conditions	Yes/no
9.	Patient not requiring long-term anticoagulation for other coexisting medical conditions	Yes/no
10.	Patients willing for surgery and regular follow-up for device programming	Yes/no

thickness: 2.0 mm; matrix: 256×256; TR: 9.7 milliseconds). Before commencing the procedure, application of the stereotactic frame (Leksell frame) was done under scalp block if surgery was planned awake or under GA in selected patients (►**Figs. 1** and **2**). The stereotactic frame was placed parallel to the orbit-meatal line to approximate the anterior commissure–posterior commissure (AC-PC) plane. A thin-cut stereotactic computed tomography (CT; 2-mm slices with no gap and no gantry tilt) was obtained. Thereafter the DBS MRI protocol and CT brain images were fused using computer software (Frame-Link software; Medtronic, Inc., Medtronic StealthStation S7 and S8 surgical navigation system).

Procedure and Course in the Hospital and Follow-Up
The surgical approach used for STN-DBS has evolved. For frame-based DBS since 2013, three software navigation systems have been used: Frame-Link software (Medtronic, Inc.) till 2018, Medtronic StealthStation S7 navigation system in 2019, and Medtronic StealthStation S8 DBS software starting in 2020. Based on the navigation system, the anatomical STN targeting, trajectory planning, selection of entry point (marked), and the stereotactic frame setting were done (►**Fig. 3**). By altering the navigation system, there was no effect on the operating techniques, the lead's final placement, or the clinical outcome. However, the procedure was significantly simpler because of the upgradation of the tool. A burr hole was made at the chosen entry point. Fibrin glue was administered after dural opening to restrict cerebrospinal fluid (CSF) egress that could potentially lead to brain shift and malposition of leads. Microelectrode drive was then attached with the stereotactic frame, which enabled microelectrode recording (MER) and microstimulation by a trained neurophysiologist (►**Fig. 3**). Platinum-iridium glass-coated microelectrodes having an impedance of roughly 0.3 to 0.5 ohm (Ω) were used for microelectrode mapping. These platinum-iridium microelectrodes can record single units of activity and are used for microstimulation of up to 100 mA without significant quality degradation of the recording.

Fig. 1 Application of stereotactic frame before computed tomography (CT) scan of a patient undergoing awake surgery.

Fig. 2 Brain imaging with a stereotactic frame of a patient undergoing surgery under general anesthesia.

Additionally, it was used to locate the STN, clinical effects, and possible side effects. Thereafter, a C-arm fluoroscopy was used to confirm the final electrode placement. The same was repeated on the opposite side. Following this, the leads were connected to the pacemaker and implantation was done in the subclavicular subcutaneous space. Using a DBS programmer,

impedance check and programming were reconfirmed based on the patient's clinical response. We switched from a five-channel MER to a single central MER, as our experience and expertise improved and occasionally to a second channel, depending on the outcomes of the first MER.

Antiparkinsonian drugs were initiated at the earliest through Ryle's tube in patients undergoing surgery under GA. Each patient underwent an immediate postoperative noncontrast CT of the brain; these images were then merged with the preoperative MRI using StealthStation S8 to check for best leads contacts and stimulation. Each patient was closely monitored in the intensive care unit (ICU) for possible clinical complications. The pacemaker was initiated in a low setting, 48 hours from the time of surgery, in patients without any clinical deterioration. Patients with an uneventful stay in the ward were discharged after a week with a plan to follow up in the outpatient department (OPD) after 2 weeks. Postoperatively each patient was initiated on limb, speech, and swallowing therapy, based on their clinical condition. In the OPD, pacemaker programming was done as per the individual's clinical situation. Variables that were used as programming parameters included the following: contact selection, mode of stimulation (monopolar/bipolar/tripolar), the intensity of current (voltage), pulse width (microseconds), and frequency (hertz).

Variables

The clinical information (preoperative and postoperative) about these patients was extracted from the hospital's medical record. Factors such as UPDRS III motor examination items 18, 20, 21, 22, 29, 30, and 31 and UPDRS IV items 1 and 36 to 39 were included and coded. These were recorded in a standard data abstraction sheet (Microsoft Excel, version 16.66.1) and thereafter analyzed.
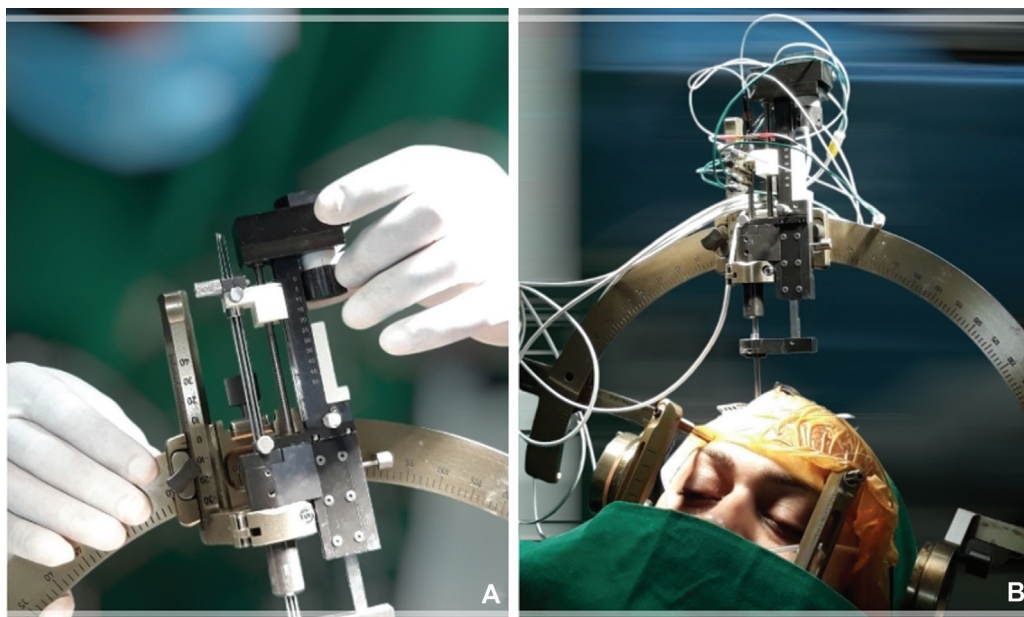

Fig. 3 (A) Microelectrode drive was attached with stereotactic frame for recording. (B) Microelectrode recording (MER) and microstimulation through a microelectrode drive.

Due to the retrospective nature of the study, not revealing an individual's name or images, a waiver of consent was obtained from the institute's review board.

Results

A total of 53 patients were operated on during the study period of 9 years. The mean age of the study population was 60.5 (SD: 8.2) years, of which the majority were males (33 [62.3%]). The majority (48 [90.6%]) had a 10-year average duration of disease (►Table 2). The most predominant symptoms included rigidity and hypokinesia (27), severe dyskinesia (21), and tremors (17; ►Table 2). A preoperative UPDRS component III (mainly motor) and component IV (complications of therapy) evaluation was done for each participant. A comparison between the preoperative and

postoperative outcomes at 6 months based on UPDRS is given in ►Table 3. The average preoperative levodopa dosage was 900 mg/d and the average duration of motor fluctuation and dyskinesia was approximately 5 years. To observe the clinical effects during awake surgery, no antiparkinsonian medication was administered on the morning of the surgery. The majority (45 [84.9%]) of these received a bilateral monopolar simulation, whereas 3 patients (5.7%) received bilateral bipolar stimulation. Unilateral bipolar stimulation was used in five (9.4%) patients (►Table 2). The mean stimulation voltage was maintained at 2.8 mA (range: 1–3 mA), the mean pulse width was maintained at 90 microseconds (range: 60–110 microseconds), and the mean rate ranged from 90 to 140 Hz. At 6 months of follow-up, improvement in UPDRS component III (mainly motor) was noted in the majority (36 [67.9%]) of the cases (►Table 3).

Table 2 Baseline characteristics, predominant symptoms, and surgery-related details

Sl. no.	Variables (total population: 53)	Frequency (%)	
1.	Mean age (SD), y	60.5 (8.2)	
2.	Males	33 (62.3)	
3.	Females	20 (37.7)	
4.	Duration of symptoms (SD), y	8.1 (3.4)	
5.	Coexisting disease (s)		
(i).	Diabetes mellitus	21 (39.6)	
(ii).	Hypertension	33 (62.3)	
(iii).	Ischemic heart disease	6 (11.3)	
(iv).	Past history of cerebrovascular accident	3 (5.7)	
(v).	Reactive airway disease (asthma/chronic obstructive pulmonary disease)	2 (3.8)	
(vi).	Chronic kidney disease	0 (0.0)	
(vii).	Chronic liver disease	0 (0.0)	
(viii).	On anticoagulation due to other medical illness	0 (0.0)	
(ix).	Coexisting disease ($\leq$ 2)	19 (35.8)	
(x).	Coexisting disease ($>$ 3)	3 (5.7)	
6.	Predominant symptoms and outcome	Preoperative symptoms	Postoperative outcome (significant improvement)
(i).	Rigidity and hypokinesia	27 (50.9)	21 (77.8)
(ii).	Severe dyskinesia	21 (39.6)	16 (76.2)
(iii).	Tremors	17 (32.1)	12 (70.6)
7.	Surgeries done under general anesthesia	6 (11.3)	
8.	Awake surgeries done under scalp block and local anesthesia infiltration	47 (88.7)	
9.	Subthalamic deep brain stimulation details	N/A	
(i).	Bilateral monopolar simulation	45 (84.9)	
(ii).	Bilateral bipolar stimulation	3 (5.7)	
(iii).	Unilateral bipolar stimulation	5 (9.4)	
10.	Neuro intensive care stay (SD), d	1.9 (3.2)	
11.	Hospital stay (SD), d	9.2 (5.9)	

Abbreviation: SD, standard deviation.

Table 3 Comparison between preoperative and postoperative outcomes based on Unified Parkinson's Disease Rating Scale

Variables	Preoperative		Postoperative	
	Medications OFF (average)	Medications ON (average)	Medications OFF (average)	Medications ON (average)
Speech[a]	2	1	1	0 → 1
Tremors[b]	8	4	2	1
Rigidity[c]	4	2	2	1
Gait[d]	4	3	1	1
Postural stability[e]	3	3	1	1
Akinesia[f]	4	3	1	1
Dyskinesia[g]	–	12	–	2
Clinical fluctuations[h]	–	6	1	1
Stand–walk–sit test (seconds)	44	16	18	14
No. of steps	70	25	30	22

Abbreviations: UPDRS, Unified Parkinson's Disease Rating Scale.
[a]UPDRS III (motor examination): item 18
[b]UPDRS III (motor examination): item 20 and 21—tremor at rest, head (face, lips, and chin), right and left hand, right foot and left foot, action, or postural tremor of the right and left hand.
[c]UPDRS III (motor examination): item 22—rigidity of the neck, right upper extremity, left upper extremity, right lower extremity, and left lower extremity.
[d]UPDRS III (motor examination): item 29.
[e]UPDRS III (motor examination): item 30—response to sudden, strong posterior displacement produced by pull on shoulders while the patient is erect with eyes open and feet slightly apart.
[f]UPDRS III (motor examination): item 31—bradykinesia and hypokinesia.
[g]UPDRS IV (complications of therapy): item 1.
[h]UPDRS IV (complication of therapy): items 36–39.

Rigidity and hypokinesia (21), severe dyskinesia (16), and tremors (12) improved significantly in many patients during the immediate hospital stay (►Table 2). ►Fig. 4 shows the preoperative and postoperative (at 3 months of follow-up) images of a 63-year-old doctor, who presented to us in a bed-bound condition (severe rigidity of all limbs and hypokinesia), who benefitted from an STN-DBS. ►Fig. 5 illustrates the preoperative MRI/CT images and the postoperative MRI/CT fusion images (using Medtronic StealthStation S8 DBS software) of this patient.

Two patients developed a small cerebral hematoma along the lead track leading to hemiparesis, which resolved spontaneously with supportive care. Two patients developed surgical site infection at the infraclavicular region (battery placement site) that warranted debridement and intravenous antibiotics. However, the patient improved (presenting complaints as well as the surgical site infection) and is presently doing well. One patient had kinking of the lead in the battery placement site and required a refix following which he improved drastically. While in the ICU, one patient developed pneumonia and severe septicemia with no response to IV antibiotics. He developed neuroleptic malignant syndrome and succumbed to his illness on post-op day 4.

Discussion

This is the first study done on the Indian population undergoing STN-DBS for PD to assess the outcome and add it to the literature database. STN-DBS has established a strong reputation as an effective treatment option for some PD patients since it was first used in humans more than 15 years ago. After the FDA approval in 1997, this technology has experienced a revolution in the last 10 years, including more sophisticated stimulation delivery with new devices as well as surgical targeting.[14] Targeting deep nuclei more precisely has become possible, thanks to the use of intraoperative imaging, merging software and MER.[15,16] STN-DBS is a highly effective treatment for all cardinal symptoms, including akinesia, rigidity, tremor, and postural instability, as well as those secondary to complications (levodopa) to therapy.[17] The dorsolateral motor portion of the STN may produce the best results, but there is evidence that zona incerta stimulation also has a positive impact.[18] Typically, STN-DBS should be carried out bilaterally to improve motor symptoms on both sides and hence enable the maximum medication reduction as done for our patients.[11,15,17]

Many of these patients (43 [81.1%]) were referred from our center's movement disorder OPD. However, the selection of patients as potential candidates for surgery was decided by the team of neurosurgeons/neurologists and neuropsychiatrists based on the "10-point" criteria developed at our center after a thorough literature research.[13,17,19,20] Based on this 10-point criteria, we suggests general neurologists practitioners to identify candidates for early STN-DBS surgery and refer to center with facility. Our study showed that almost two-thirds (67.9) of the operated cases had an

Fig. 4 (**A–C**) Preoperative images showing severe rigidity of all limbs and hypokinesia of a patient undergoing subthalamic deep brain stimulation and (**C–E**) postoperative outcome (ambulant without support).
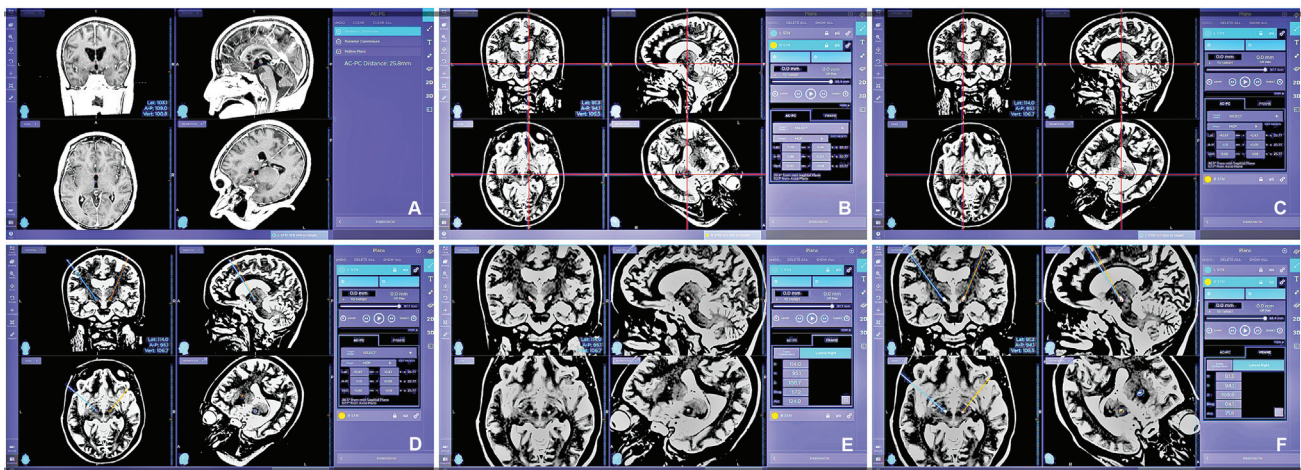

Fig. 5 (**A**) Magnetic Resonance imaging (MRI)-T1 weighted image (T1WI) showing anterior commissure (AC) and posterior commissure (PC). Distance between the AC and PC: 25.8 mm: midline set using Medtronic - Stealth Station™ S8 - DBS software. (**B, C**) MRI-T2 weighted image (T2WI) showing the location of the subthalamic nucleus (STN) and red nucleus; using the direct/indirect targeting method, the desired target point at the dorsolateral part of STN was selected. (**D**) MRI-T2WI revealing bilateral STN targeting points; (**E, F**) MRI-CT fusion images (using Medtronic - Stealth Station™ S8 - DBS navigation software) to check the location of the leads and trajectory post-operatively.

improved motor (UPDRS III) at 6 months of follow-up. Kleiner-Fisman et al published the largest cohort of 921 patients who had a motor improvement (UPDRS III) of approximately 52%, with a decrease in OFF time for 68.2% after undergoing STN-DBS (6 months).[21] Several randomized control trials and systemic review by Hamani et al[22] in 2005 in 471 patients, Deuschl et al[23] in 2006 in 156 patients, and Weaver et al[24] in 2009 in 255 patients undergoing STN-DBS showed almost similar clinical outcomes and improvement of UPDRS III (motor functions): 56 to 49, 41, and 29%, respectively. These superior outcomes could be because of three main reasons: (1) process of patient selection, (2) iterative technological advancements that led to advancements in patient-specific target identification and cutting-edge surgical techniques for electrode placement, and (3) recent developments in targeting methods based on imaging and MER reviewing. Both improved MER-based techniques and evolving imaging-based targeting paradigms have demonstrated excellent results.[25] Additionally, a small sample size with less follow-up time can also contribute to these results. Surgery-related complications were seen in five (9.4%) cases, which are consistent with the previous studies done by Hamani et al,[22] Tir et al,[26] Seijo et al,[27] and Voges et al.[28] These findings were similar to studies with smaller sample size as well, where the complication rate remained lower than 10%.[29,30]

New working paradigms have emerged because of these ongoing technological advancements. DBS will remain useful in the management of PD and other complex movement disorders. For the clinical management of patients who opted for this therapy, it is crucial to have a clear understanding of the underlying principles, appropriate patient selection, intended brain targets, technical aspects of programming the device, the effectiveness of this treatment in PD, and its potential complications. An experienced team of neurosurgeons, neurologists, neuroradiologists, and support staff who are committed to the treatment can achieve the best results.

Conclusion

In view of these findings, STN-DBS appears to be a good, safe, and effective treatment for a subset of medically refractory PD with an overall improvement in two-thirds of the population and about 10% risk of complications, which is comparable to previous research. Benefits and potential negative outcomes should not be overemphasized or underemphasized because reports of surgical complication rates and long-term side effects of DBS can vary and are inconsistent.

Limitations of our study: Owing to the retrospective nature of our study, many determinants could not be included, and the data presented here are solely based on in-and-out hospital medical records of the patients where uniformity of data was uncertain. UPDRS is a user interface scoring system; therefore, the reliability of the same is challenging. Many patients could not be contacted over the phone; hence, their long-term outcome (i.e., > 6 months) could not be

included, coded, or analyzed. Additionally, it is because of the small sample size and retrospective nature of the study that a statistical analysis with regard to the surgical outcome could not be performed.

Scope of future research: The pedunculopontine nucleus (PPN) is one of the newer targets for DBS in PD that is emerging to treat symptoms such as postural instability and gait difficulty that does not respond to STN stimulation, data on which are scant. DBS for PD is an established treatment, and methods and tools for implementing this treatment will undoubtedly advance in the coming decades, which necessitates the need for more research to demonstrate the clinical utility in future.

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