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Deep Brain Stimulation in Parkinson's Disease

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Stereotactic surgeries for movement disorders were introduced in the 1950s (1,2) but were not widely accepted due to significant morbidity, mortality, and limited knowledge in target selection for symptomatic benefit. In the late 1950s and early 1960s there was an increase in the number of stereotactic surgeries performed. With advances in pharmacological therapy, particularly the availability of levodopa, these surgeries were rarely performed until the late 1980s. Currently, based on the recognition of the limitations of drug treatments for Parkinson's disease (PD) and a better understanding of the physiology and circuitry of the basal ganglia, there has been a marked increase in surgical therapies for PD. In addition, advances in surgical techniques, neuroimaging, and improved electrophysiological recordings allow stereotactic procedures to be done more accurately, leading to reduced morbidity. Over the last decade, deep brain stimulation (DBS) is increasingly replacing lesion surgery as the preferred procedure. DBS in PD is associated with three targets: the ventral intermediate nucleus (VIM) of

the thalamus, the globus pallidus interna (GPi), and the subthalamic nucleus (STN).

HISTORY

Benabid and coworkers were the pioneers of DBS surgery. In the late 1980s, Benabid and colleagues (3), during thalamic lesioning, observed that stimulation at the site of the lesion could induce either an increase or a reduction in tremor amplitude. They noted that low-frequency stimulation increased tremor and frequencies above 100 Hz were able to alleviate tremor. They extended these observations by implanting an electrode in the contralateral motor thalamus of a patient who had undergone thalamotomy and needed surgery on the second side. This was done due to the higher rate of complications known to occur with bilateral lesion surgeries. These results were satisfactory, and soon thalamic stimulation was increasingly used instead of thalamotomy even in patients undergoing unilateral procedures. These methods have been now used in the GPi and STN to deliver high-frequency stimulation instead of creating lesions in those nuclei.

DEEP BRAIN STIMULATION HARDWARE

The Activa® Tremor Control therapy and the Activa® Parkinson Control therapy are approved therapies in the United States and Europe. These devices and other hardware have undergone multiple changes since they were first introduced. Presently the implanted hardware is manufactured by Medtronic, Inc. (Minneapolis, MN). The Activa Tremor Control and Parkinson Control therapies consist of a DBS lead, an extension wire that connects the DBS lead to an implantable pulse generator (IPG), and the neurostimulator. There are two DBS leads available. The intracranial end of both leads has four platinum-iridium contacts. One lead has contacts that are separated by 1.5 mm (Model 3387 DBS lead) and the second lead has contacts that are separated by 0.5 mm (Model 3389 DBS lead). The DBS leads are connected to the neurostimulator by the extension wire that is tunneled under the skin. There have been multiple models of stimulators that have been used for Activa therapy. The Itrel II® Neurostimulator, Model 7424 was initially used. The Soletra® Model 7426 and Kinetra® are the two neurostimulators presently available. The Kinetra has the advantage of using one stimulator to control both sides, instead of two separate Soletra neurostimulators, one for each side. The neurostimulators are typically implanted subcutaneously in the infraclavicular area. The neurostimulators can be programmed for monopolar stimulation or bipolar stimulation. Adjustable parameters include pulse width, amplitude, stimulation fre-

quency, and the choice of active contacts. The patient can turn the stimulator on or off using a hand-held magnet or using Access Review®, which also has a feature to tell the patient if the neurostimulator is on or off. The typical stimulation parameters are stimulation frequency of 135–185 Hz, pulse width of 60–120 μs, and amplitude of 1–3 v.

ADVANTAGES AND DISADVANTAGES OF DBS

The advantages of the DBS system include no destructive lesion in the brain, adjustment of stimulation parameters to increase efficacy or reduce adverse effects, bilateral operations with relative safety and reduced adverse effects, and the potential use of future neuroprotective therapies when available. The disadvantages include cost of the system, time and effort involved in programming the system, repeat surgeries related to device problems, use of general anesthesia to implant the stimulator, and battery replacement every 3–7 years.

DEEP BRAIN STIMULATION OF THE THALAMUS

Efficacy Studies

DBS of the thalamus is increasingly replacing thalamotomy as the preferred surgery for the treatment of medication resistant PD tremor. There are multiple reports regarding the efficacy of these procedures for parkinsonian tremor (Table 1) (4–17). The majority of the studies have reported that even though tremor is markedly improved, this often does not result in improvement in activities of daily living. As DBS of the thalamus does not improve bradykinesia, rigidity, or drug-induced dyskinesias, this procedure should be restricted to PD patients whose major disability is tremor.

TABLE 1 Selected Studies of Deep Brain Stimulation of the Thalamus

Author	Number of implants	Tremor improvement (%)	Follow-up (months)
Benabid et al. (7)	111	63	6
Blond et al. (5)	10	70	17
Albanese et al. (14)	31	68	8
Koller et al. (10)	24	91	12
Ondo et al. (11)	9	95	3
Limousin et al. (9)	74	85	12
Albanese et al. (14)	27	92	9
Lyons et al. (17)	9	87	40

There are very few randomized, controlled trials of thalamic DBS in PD. Open-label evaluations have indicated that 65–95% of patients have improvement in tremor (5,6,8,9). Studies with randomized, blinded evaluations have confirmed the results of unblinded studies. (10,11). The majority of the studies evaluated the efficacy of unilateral thalamic stimulation. The usual outcome variable was the clinical tremor rating scale with severity ratings of 0–4, where 0 is no tremor and 4 is severe tremor.

Benabid and colleagues have had the most experience with DBS of the thalamus. In 1997, they reported 80 PD patients who had DBS of the thalamus for drug-resistant tremor (12). The tremor was predominant at rest but persisted during posture holding and action. Bradykinesia and rigidity were mild in the majority of the patients. At the last follow-up (up to 7 years, mean 3 years) global evaluations showed the best control for parkinsonian rest tremor and the least satisfactory control for action tremor. There was no dramatic effect on other symptoms like bradykinesia, rigidity, or dyskinesias.

Koller et al. (10) reported the results of a double-blind multicenter study in 24 PD patients who had undergone unilateral thalamic stimulation. At 1 year there was a significant tremor improvement, although activities of daily living as measured by the Unified Parkinson's Disease Rating Scale (UPDRS) were not significantly changed. Results of blinded evaluations performed at 3 months were similar to the open-label evaluations.

In another multicenter trial, Limousin et al. (9) reported 57 PD patients who had undergone unilateral implant and 16 PD patients who had undergone bilateral implants. At 12 months, tremor and bradykinesia were significantly reduced by stimulation as compared to baseline. There was a 74% reduction in tremor, 16% reduction in rigidity, and 34% reduction in bradykinesia on the treated side. These improvements in rigidity and bradykinesia are not consistently reported in other studies. They did not observe any improvements in axial symptoms. Speech, postural instability, and gait were not affected by unilateral or bilateral surgery. Levodopa-induced dyskinesias were slightly but not significantly reduced. Adverse effects were reported for the entire cohort of patients, including essential tremor (ET) patients. Three patients had subdural hematomas, one of whom also had a thalamic hematoma. Two patients had infection of the system, and in five patients the electrode was replaced because of unsatisfactory results. Stimulation-related adverse effects were mild.

Ondo et al. (11) reported 19 PD patients with severe tremor, PD patients reported an 82% reduction in contralateral tremor and significant improvement in disability and global impressions. They did not find any meaningful improvement in other motor aspects of the disease, and the

activities of daily living did not change. They also performed blinded PD assessments, which resembled the unblinded outcomes. There were no significant surgical complications, and two patients had breakage of the extension wire.

Bilateral Studies

There is a lack of adequate data regarding bilateral thalamic stimulation in PD. Ondo et al. (13) reported eight patients who underwent bilateral thalamic stimulation for PD. The main cause of disability in the patients was tremor with relatively little bradykinesia and rigidity. After the second implantation, three patients reported marked improvement, two reported moderate improvement, one reported mild improvement, one patient had no change, and one patient was mildly worse. Although there was a significant improvement in tremor after the second procedure, bradykinesia, gait, and balance scores were worse. Similarly, activities of daily living scores and adverse effects were worse after the second procedure.

Long-Term Studies

Long-term results of DBS of the thalamus are not widely reported. Albanese et al. (14) reported 27 PD patients (6 with bilateral implants) with DBS of the thalamus. The longest follow-up was 2 years with a mean follow-up of 0.9 years. Tremor was completely or almost completely suppressed in 78%, unchanged in 15%, and slightly reduced in 7% of the patients. Moderate relief of bradykinesia was reported in three patients, and antiparkinsonian medications were reduced in 26% of the patients. There was one intracranial hemorrhage, one skin erosion, one electrode breakage, two infections, and two lead replacements. Kumar et al. (15) described seven PD patients with a mean follow-up of 16.2 months, and Hariz et al. (16) reported 22 PD patients with a mean follow-up of 21 months. Both studies reported long-term improvement in tremor scores. Lyons et al. (17) reported the results of 12 PD patients with a mean follow-up of 40 months and a maximum follow-up period of 66 months. Although tremor scores continued to be improved by 87%, there was a worsening of the motor UPDRS scores, suggesting the worsening of other parkinsonian symptoms. Lead repositioning occurred in two patients, and neurostimulator and extension wire replacement in one patient due to shocking sensation.

Tremor Rebound

Some authors have reported frequent tremor rebound upon turning the stimulation off (7,16,18), while others denied occurrence of such rebound

(19). Albanese et al. (14) reported a paradoxical increase of tremor in 22% of the patients when the stimulation was turned off. Similarly, Hariz et al. (16) reported that persistent tremor rebound occurred in 32% of the PD patients. Kumar et al. (15) reported tremor rebound in 57% when turning the devices off, and these patients had to continuously use stimulation. Although the cause of rebound is not known, it could be related to disease progression or tolerance to stimulation. Kumar et al. (15) speculated that rebound could be due to the removal of the inhibitory effect on the VIM nucleus provided by stimulation and likely represents habituation.

Tolerance to Chronic Stimulation

A gradual loss of tremor benefit over time when the stimulation parameters are kept constant suggests tolerance to chronic stimulation (15). Although increases in parameters can initially result in benefit, in patients with a true tolerance phenomenon the increased stimulation parameters lead to adverse effects without further benefit. Occasionally, a stimulation holiday may improve the tolerance phenomenon, but in the majority of patients this is a temporary improvement. Although the exact mechanism of tolerance is not known, Kumar et al. (15) postulated that tolerance could be secondary to progression of the underlying disease, loss of a microthalamotomy effect over time, habituation of the neuronal network, and an increase in impedance at the stimulating tip.

Patient Selection

With the advent of other target sites for PD, the role of thalamic stimulation in PD has been reduced significantly. Presently, thalamic stimulation should be restricted in PD patients with a combination of PD and essential tremor, elderly patients (greater than 80 years of age) in whom the major disability is tremor, and patients with medication-resistant tremor in whom a definitive diagnosis of PD cannot be established. In general, patients should not have any significant cognitive impairment, significant comorbidities, or a cardiac pacemaker.

DEEP BRAIN STIMULATION OF THE GLOBUS PALLIDUS

Efficacy Studies

Surgery targeting the internal segment of the GPi improves the cardinal features of PD. Lesion surgery and DBS of the GPi appear to improve tremor, bradykinesia, rigidity, and dyskinesias. Due to concerns about

severe complications related to bilateral lesions, DBS of the GPi is preferred to pallidotomy.

Siegfried and Lippitz were among the first to report the use of DBS for continuously stimulating the ventroposterolateral pallidum. They implanted bilateral GPi electrodes in three PD patients. Follow-up in these three patients ranged from 3 months to 1 year. They reported improvement in Webster Rating Scale scores and on-off motor fluctuations.

Since then, multiple studies have reported the efficacy of GPi stimulation for PD (see Table 2). All studies reported a small number of patients, and follow-up has ranged from days to a maximum of 30 months. The patients have been implanted unilaterally and bilaterally. The improvement in the off medication state in activities of daily living ranged from 19 to 68%, and the UPDRS Motor score improvement ranged from 24 to 50%. The improvement in activities of daily living in the on medication state ranged from 22 to 60%, and UPDRS Motor scores ranged from 1 to 60%. All studies reported significant reductions in dyskinesias, resulting in improvement in on time during the day.

Pahwa et al. (22) reported five PD patients who underwent pallidal stimulation. Three patients had bilateral implants, and two had unilateral implants. Four patients were markedly improved, and one was moderately improved after surgery. The activities of daily living subscores of the UPDRS improved by 19% in the off-medication state and by 42% in the on-

TABLE 2 Selected Studies of Deep Brain Stimulation of the Globus Pallidus

Author	Number of patients	Follow-up	UPDRS improvement
Pahwa et al. (22)	3 unilateral 2 bilateral	3 months	off scores: ADL 19%, Motor 24% on scores: ADL 41%, Motor 60%
Gross et al. (54)	7 unilateral	1–3 years	off scores: Motor 30% on scores: Motor 43%
Krack et al. (55)	5 bilateral	3–6 months	motor 39%
Kumar et al. (56)	4 unilateral/4 bilateral	3–6 months	off scores: ADL 26%, Motor 27%
Ghika et al. (26)	6 bilateral	24 months	off scores: ADL 68%, Motor 50% on scores: ADL 60%, Motor 26%
Volkmann et al. (57)	9 bilateral	12 months	off scores: Motor 44%
Merello et al. (58)	6 unilateral	3 months	off scores: ADL 58%, Motor 29% on scores: ADL 22%, Motor 8%
DBS for PDSG (37)	38 bilateral	6 months	off scores: ADL 36%, Motor 33% on scores: ADL 31%, Motor 32%
Kumar et al. (24)	17 bilateral 5 unilateral	6 months	off scores: ADL 40%, Motor 32% on scores: ADL 30%, Motor 1%

UPDRS = Unified Parkinson's Disease Rating Scale; ADL = activities of daily living; DBS = deep brain stimulation; PDSG = Parkinson's Disease Study Group.

medication state. Patient diaries demonstrated an increase in on-time with a decrease in both off-time and on-time with dyskinesias.

A review by the American Academy of Neurology identified reports on 64 patients who had undergone DBS of the globus pallidus (23). An approximately equal number of patients underwent unilateral and bilateral implantations. Benefit was reported in all aspects of PD with a marked attenuation of motor fluctuations and dyskinesias. In unilateral implants, the benefits were most pronounced on the contralateral side.

Kumar et al. (24) reported 22 PD patients who were treated with either unilateral ($n = 5$) or bilateral ($n = 17$) GPi stimulation. Evaluations performed in the off-medication state at 6 months reported a 32% improvement in UPDRS motor scores, 40% improvement in UPDRS activities of daily living scores, and 23% improvement in dyskinesias. When the evaluations were repeated in the medication "on state," UPDRS motor scores improved by 1%, UPDRS activities of daily living scores improved by 30%, and dyskinesias improved by 68%.

The Deep Brain Stimulation for Parkinson's Disease Study Group reported a multinational, prospective study of bilateral GPi stimulation in PD (25). Forty-one patients were enrolled; electrodes were implanted in 38 patients (two patients had cerebral hemorrhage and one patient had intraoperative confusion). In comparison to baseline, there was a significant improvement in the UPDRS motor scores in the off-medication state and a smaller improvement in the on-medication state. In the off-medication state, all the subscales of the UPDRS also improved. Tremor scores improved by 59%, rigidity improved by 31%, bradykinesia improved by 26%, gait by 35%, and postural instability by 36%. In the on-medication state, tremor scores improved by 85%, rigidity and bradykinesia by 22%, gait by 33%, and postural instability by 50%. Patient diaries revealed that the percentage of on time without dyskinesias during the awake time increased from 28 to 64%, and the off time reduced from 37 to 24%. The mean daily dose in levodopa equivalents was unchanged between baseline and 6 months.

Long-term results of DBS of the globus pallidus have been lacking. Ghika et al. (26) reported six PD patients with a mean age of 55 years and disease duration of 16 years with a minimum follow-up of 24 months. The mean improvement in the UPDRS motor "off" scores and the ADL scores was more than 50%. The mean "off" time decreased from 40 to 10%, and the dyskinesia scores were reduced by 30%. Although the improvements persisted beyond 2 years after surgery, signs of decreased efficacy were seen after 12 months.

In summary, DBS of the globus pallidus results in improvement of the cardinal features of PD including tremor, bradykinesia, rigidity, and gait and a marked reduction of levodopa-induced dyskinesias. There is an

improvement in daily motor fluctuations. The daily levodopa dosage or antiparkinsonian medication dosage is not reduced.

Optimal Pallidal Electrode Location

Studies of GPi stimulation have reported variable and sometimes opposite effects by using different electrode contacts (27–29). Bejjani et al. (27) investigated the effect of stimulation on different sites of the globus pallidus (GP) in five PD patients. Stimulation in the dorsal GP (upper contact) significantly improved gait, akinesia, and rigidity and could induce dyskinesia when the patients were in the off-state. In contrast, stimulation of the posteroventral GP (lower contact) significantly worsened gait and akinesia. Krack et al. (28) reported similar results and suggested using an intermediate contact between the dorsal and the posteroventral contacts as a good compromise between these opposite effects.

DEEP BRAIN STIMULATION OF THE SUBTHALAMIC NUCLEUS

The STN has gained importance in PD. Although it is believed that subthalamic lesions induce ballism, patients who undergo subthalamotomy or subthalamic stimulation usually do not have these involuntary movements. In a study by Carpenter et al. (30) it was shown that in animals ballism was induced on the contralateral side if more than a minimal percentile volume of the nucleus, greater than 20%, was destroyed or the lesion was not too large or if it did not involve the adjacent structures. Hence if the lesions extend beyond the STN, and in particular if they involve the internal segment of the globus pallidus or the pallidal fugal pathways, then no involuntary movements are seen (31).

There are multiple reports of the antiparkinsonian effects of STN DBS (Table 3) (32–38). Limousin et al. (39) reported results of bilateral STN and found improvements of 58–88% in the activities of daily living subscores and 42–84% in the motor subscores of the UPDRS. Kumar et al. (40) conducted evaluations in a double-blind fashion and reported improvements of 30% in the activities of daily living and a 58% improvement in motor scores of the UPDRS. They also reported a mean reduction of 40% of antiparkinsonian medications and 83% improvement in dyskinesias.

Other studies have duplicated these results with STN stimulation. All studies have consistently reported improvement in the UPDRS scores in the off-medication state. The improvement in the ADL scores ranged from 30 to 72%, and the UPDRS Motor score improvements ranged from 42 to 74% in the off-medication state (Table 3). Irrespective of the percentage of

TABLE 3 Selected Studies of Deep Brain Stimulation of the Subthalamic Nucleus

Author	Number of patients	Follow-up	Improvement
Krack et al. (55)	8	3–6 months	UPDRS off scores: Motor 71% Medication reduction 56%
Limousin et al. (39)	24	12 months	UPDRS off scores: ADL 58%, Motor 60%, Dyskinesias 63%, Meds reduced 50%
Kumar et al. (40)	7	6–12 months	UPDRS off scores: ADL 30%, Motor 58% Dyskinesias 83%, Meds reduced 40%
Maro et al. (36)	7	16 months	UPDRS off scores: ADL 52%, Motor 42% Medication reduction 65%, UPDRS on scores: ADL 7%, Motor 5%
Molinuevo et al. (59)	15	6 months	UPDRS off scores: ADL 72%, Motor 66% Dyskinesia reduction 81%, Medication reduction 80%
Houeto et al. (60)	23	6 months	UPDRS off scores: ADL 66%, Motor 67% Dyskinesia reduction 77%, Meds reduced 61%
Rodriguez et al. (38)	15	12–36 months	UPDRS off scores: ADL 70%, Motor 74% Meds reduced 55%
Romito et al. (42)	22	1–3 years	UPDRS off scores: ADL 68%, Motor 50% Meds reduction 69%
Thobois et al. (61)	18	6–12 months	UPDRS off scores: ADL 53%, Motor 55% Dyskinesias reduction 66%, Med reduced 76%
DBS for PDSG (37)	96	6 months	UPDRS off scores: ADL 44%, Motor 51% Dyskinesia reduction 70%, Meds reduced 37%

improvement in the motor scores, these improvements are similar to those observed with the levodopa challenge. In other words, if the patient is evaluated 12 hours after not taking antiparkinsonian medications (off-medication state) and the evaluations are repeated after the patient has taken antiparkinsonian medications and the medications have started working (on-medication state), the percentage improvement would be similar to that seen after surgery with stimulation alone. This levodopa challenge predicts the response to surgery if the electrodes are in the correct position and programming of the stimulators is optimized.

The other consistent finding with STN stimulation is the reduction in antiparkinsonian medications after surgery, which results in a marked reduction in dyskinesias. Antiparkinsonian medications are usually reduced by 37–80% after surgery, resulting in a 63–81% reduction in dyskinesias (Table 3). The improvement in the off-medication UPDRS Motor scores also results in a reduction in off-time during the day.

One of the largest studies of STN stimulation is a prospective study that was performed in 18 countries (37). One hundred and two patients were enrolled, 96 of whom had electrodes implanted in both subthalamic nuclei. Bilateral procedures were not performed in 6 patients due to complications with the first procedure (intracranial hemorrhage in two, hemiparesis in one, confusion in one, lack of response in one, and improper lead placement in one). In the off-medication state there was a mean improvement of 44% in the activities of daily living and a mean improvement of 51% in the UPDRS Motor scores. All subscores of the UPDRS (off-medication state) also improved—tremor scores by 79%, rigidity by 58%, bradykinesia by 42%, gait by 56%, and postural instability by 50%. Patient home diaries revealed that the off-state during the day decreased by 61%, on-state increased by 64%, and on-state with dyskinesias decreased by 70%. Although there was some improvement in the on-state UPDRS scores, it was not as robust.

Long-term follow-up results for STN DBS are limited. Benabid et al. (41) followed more than 50 patients for one year who maintained the benefit. Thirty patients were assessed at 2 years, 16 patients at 3 years, 9 patients at 4 years, and 4 patients at 5 years. They observed adequate control of the cardinal features of PD and the reduced levodopa requirement persisted. They observed a tendency towards increased hypophonia and axial motor features. Rodriquez et al. (38) reported initial results in 15 patients after 12 months and in 9 patients between 30 and 36 months after surgery. They reported a 74% improvement in the UPDRS motor scores in the off state with a 55% reduction in the levodopa daily dose. Nine patients with long-term follow-up continued to have a 61% improvement in UPDRS motor scores and a 38% reduction in levodopa dosage. Romito et al. (42) reported on 22 patients, 7 of whom were followed up at 36 months. In the off-medication state, the UPDRS activities of daily living scores were improved by 59%, UPDRS Motor scores by 49%, and the antiparkinsonian medications were reduced by 70%.

In summary, studies of STN stimulation indicate that stimulation induces a 40–75% improvement in UPDRS motor scores in the off medication condition and all cardinal features of PD improve. UPDRS on medication motor scores are not significantly improved, but there is a 40–80% reduction in antiparkinsonian medication. Off periods and dyskinesias are also significantly improved. Activities of daily living and patient quality of life scales have also shown significant improvements in multiple studies.

PATIENT SELECTION FOR GPi AND STN SURGERY

The criteria for patient selection for these targets in PD are similar. The ideal candidate for DBS of the GPi and STN is a patient with idiopathic levodopa-

responsive PD. We recommend that patients undergo a levodopa challenge 12 hours after not taking any antiparkinsonian medications. The patients should have improvement of at least 30% in the UPDRS Motor scores after the levodopa challenge to be candidates for surgery. Patients should be under 75 years as older patients may have difficulty tolerating the procedure. Patients should have been tried on combinations of different antiparkinsonian medications, including all those currently available. Patients with disabling medication-resistant tremor or an inability to tolerate antiparkinsonian medications should be excluded. Patients should exhibit no evidence of dementia or significant cognitive abnormalities. Patients should undergo detailed neuropsychological testing. Patients should have no behavioral problems and a realistic expectation of surgery. Unfortunately, there are no tests available that would predict what kind of behavior problems would interfere with the outcome of surgery, but close evaluation by the neurologist and neuropsychologist can help exclude unsuitable patients.

WHICH LOCATION—DEEP BRAIN STIMULATION OF THE GPi OR STN?

The criteria for patient selection for GPi and STN targets are similar. A few studies have compared patients who have undergone surgeries at these targets, but most of these are not randomized studies and the number of patients in these studies is small. Krack et al. (34) retrospectively compared eight patients who were operated on the STN and five patients who were operated on the GPi. In the off-state, the UPDRS Motor score improved by 71% with STN stimulation and by 39% with GPi stimulation. Rigidity and tremor showed good improvement in both groups, but bradykinesia was more improved in the STN group. There was a reduction in levodopa dosage only in the STN group. Burchiel et al. (35) performed a randomized blinded prospective study in 10 PD patients with 5 patients randomized to GPi and 5 to STN stimulation. At 12 months in the off-state both groups demonstrated a 40% improvement in the UPDRS Motor scores. Dyskinesias were reduced in both groups, although the antiparkinsonian medications were only reduced in the STN group. In another study, Scotto di Luzio and colleagues (43) compared nine patients who had undergone bilateral STN stimulation to five who had undergone GPi stimulation. STN stimulation was superior to GPi stimulation in the reduction of the clinical features and the decrease in medication off-state. There was a reduction in levodopa dose only in the STN group. Volkmann et al. (44) retrospectively compared 16 patients who had undergone STN stimulation with 11 patients who had undergone GPi stimulation. There was a 54% improvement in the UPDRS Motor scores with GPi stimulation as compared to 67%

improvement with STN. Medication was reduced only in the STN group, and they required less electrical power compared to the GPi group. Finally Krause et al. (45) prospectively compared 6 GPi patients with 12 STN patients. Although STN stimulation improved Schwab and England scores, GPi stimulation did not improve these scores. GPi stimulation directly reduced the dyskinesias, whereas STN stimulation reduced the dyskinesias due to reduction in antiparkinsonian medications. STN stimulation improved the UPDRS Motor scores; GPi stimulation did not have a similar effect. These and other noncomparative studies show a greater improvement in patients who have undergone STN stimulation as compared to GPi stimulation, hence the majority of the surgery centers favor STN stimulation over GPi stimulation.

ADVERSE EFFECTS OF DBS

Complications of DBS are relatively similar in the three groups (VIM, GPi, and STN) and can be divided into those related to the surgical procedure, those associated with the device, and those associated with stimulation. These complications are also related to the expertise of the personnel, the proper patient selection, and the mechanical failure of the equipment.

Surgical

Surgical complications are those that occur within 30 days of surgery. These complications are typical of those seen with other intracranial stereotactic procedures and occur in less than 5% of the patients. These complications include hemorrhage, ischemic lesions, seizures, and infections. Pollack et al. (46) assessed 212 patients who had undergone STN, GPi, or VIM DBS. Two patient deaths could be indirectly related to surgery. One occurred 2 weeks after surgery and was due to pulmonary embolism, and another occurred 3 years after surgery in a patient who developed a frontal hematoma during surgery. In this series, permanent severe morbidity occurred in seven patients (2.3%): three patients who had intracerebral hematoma during surgery, three patients who had worsening of cognitive status leading to dementia, and one patient due to an unrelated traumatic hematoma. Intracranial hematoma is one of the most severe complications of stereotactic surgery. In the series by Pollack et al. (46) there was a 4.2% risk of intracranial hemorrhage. In another large series there was a 4.8% risk of intracranial hemorrhage (37). The risk of infection is usually less than 5%. Other transient events include seizures, confusion, subcutaneous bleeding, dysarthria, nonhemorrhagic hemiparesis, and brachial plexus injury. The majority of these events are transient and resolve within 30 days.

Hardware-Related

Device-related events include misplacement or displacement of the electrode, skin erosion, fracture of electrode or its components, and mechanical problems with the electrical system. These device-related events can occur in up to 25% of the patients (47). Oh et al. (47) reported 79 patients who had received 124 electrode implants. Overall, 20 patients (25.3%) had hardware complications. These included four lead fractures, four lead migrations, three short or open circuits, 12 erosions or infections, and two foreign body reactions. The most frequent complication was related to electrode connectors. Pollack et al. (46) in their series of 300 patients reported that infection or cutaneous erosion occurred in 10 patients, breakage of lead connection in 7 patients, and stimulator repositioning in 5 patients. In another series (37), out of a total of 143 patients, lead migration occurred in 5 patients, infection in 4 patients, lead breakage in 2 patients, lead erosion in one patient, and intermittent function in one patient.

Stimulation-Related

Stimulation-related adverse effects depend on the exact location of the active electrode contact and the intensity of stimulation. The majority of these adverse effects can be reduced by either using another electrode contact or reducing the stimulation intensity. These adverse effects include eye lid closure, double vision, dystonic posturing, dysarthria, dyskinesias, paresthesia, limb and facial muscle spasms, depression, mood changes, visual disturbances, and pain. Occasionally nonspecific sensations like anxiety, panic, palpitations, nausea, and strange sensations can also occur. If these adverse effects persist, this usually indicates that the electrode is not in the ideal position.

MECHANISM OF ACTION

The exact mechanism of action of DBS is unknown. As the effects observed after stimulation are similar to those observed after ablation in the thalamus, GPi, and STN it was believed that DBS acts by suppressing neuronal activity and decreasing the output from the stimulated site. In addition, DBS of the GPi or pallidotomy produce similar changes in the cortical metabolic activity as measured by positron emission tomography (48,49). Electrophysiological studies such as those of Benazzouz et al. (50) reported that after 5 seconds of stimulation of the STN nucleus in rats at the usual parameters used in humans, the STN neurons were inhibited for several hundred seconds and the entopeduncular nucleus (corresponds to

GPi in humans) is strongly depressed and the GP (corresponds to GPe in humans) is excited. They believed that inhibition of the STN occurs due to local inhibitory effect of the high-frequency stimulation.

Although the above data might suggest that electrical stimulation inhibits neuronal activity and decreases neuronal output from the stimulated structure, other data support the hypothesis that electrical stimulation leads to increased output from the stimulated structure, suggesting that activation plays a role. Windels et al. (51) studied the effects of STN stimulation in rats and found that there were increased levels of glutamate suggesting activation of glutamatergic output from the STN. Hashimoto et al. (52) also demonstrated increased discharge rates of neurons in the GPi during chronic STN stimulation with resultant improvement in motor signs. In addition, it has been shown that there is an irregular pattern of neuronal activity present before stimulation, which changes to a tonic activation pattern of the GPi during STN stimulation. Also, Montgomery and Baker (53) used computer simulations that modeled the effect of different frequencies and regularity of neuronal activity. The simulations suggested that irregular activity in the neurons converging with other neurons could result in a loss of information transfer. They suggested that the therapeutic effect of DBS could be due to driving neurons at higher and perhaps more importantly at regular frequencies that result in improvement of the symptoms due to regularity of the neurons.

CONCLUSION

DBS of the thalamus is indicated for PD patients with medication-resistant tremor with minimal bradykinesia or rigidity. DBS of the GPi or STN is indicated for patients with motor fluctuations and dyskinesias. All cardinal signs and symptoms of PD improve with DBS of the GPi and STN. The PD medications can be reduced with DBS of the STN but not with DBS of the GPi. All these procedures have very low risk of morbidity, although device-related events could lead to repeat surgery in some patients.

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