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Review Article

The advances of Deep Brain Stimulation (DBS) for treatment of Parkinson's disease (PD)

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ABSTRACT

Advanced Parkinson's disease (PD) is characterized by the presence of motor fluctuations, various degrees of dyskinesia, and disability with functional impact on daily living and independence. Therapeutic management aims to extend levodopa (L-DOPA) benefit while minimizing motor complications and includes, in selected cases, the implementation of drug infusion and surgical techniques. The concept of deep brain stimulation (DBS) for PD was introduced over 20 years ago, but our understanding of the nuances of this procedure continues to improve. This review aims to demonstrate the advances of DBS in the treatment of PD patients.

Keywords: *Deep brain stimuation; previous pallidotomy; microrecording; Parkinson disease*

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Parkinson's disease (PD) was first described in the 19th century by James Parkinson. The disease is neurodegenerative, chronic, and progressive. PD is caused by an intense decrease in the production of dopamine, which is an important neurotransmitter in the performance of voluntary movements of the body automatically, especially in the substantia nigra of the midbrain[1].

The disease is characterized by cardinal signs of stiffness, akinesia or bradykinesia, tremor and postural instability. Although it presents an idiopathic etiology, it is believed that its main triggers come from environmental and genetic factors, and may interact to the neurodegenerative development in focus. Some cases of PD are accompanied by other comorbidities, such as: depression, psychosis, hyposmia, weight loss or dementia. The incidence of the disease is approximately 0.15%. There is a higher proportion in the population over 60 years old. The aging process is closely intertwined with this disorder due to the acceleration of the loss of dopaminergic neurons over the years[2].

The basal ganglia (BG) are fundamental in understanding the pathophysiology of PD. The hyperactivity of the Subthalamic Nucleus (STN) generates several of the clinical motor signs of PD. However, if STN is injured, it can also increase the risk of developing psychiatric disorders, balism and dyskinesias. Another important nucleus in PD is the Globus Pallidus (GP), mainly on the internal portion (GPi). Understanding the activity of these two structures and their lesions is of paramount importance to neurologists and neurosurgeons[3].

There are many pharmacological treatments that are effective to reduce the PD symptoms, especially levodopa (L-DOPA). However, the long-term motor levodopa-induced adverse effects are very common. Patients with advanced PD symptoms can be benefited for surgical procedures, including the implantation of electrodes in BG for continuous electric stimulation, "deep brain stimulation" (DBS)[4]. This technique was introduced in the 1990s and is accepted as an effective treatment for patients with PD, mainly in the advanced stage[5].

The extent of benefit is similar for young and old patients, although adverse events tend to be higher in older patients. For patients younger than 75 years with advanced PD, DBS is more effective than medical therapy in improvement of quality of life. DBS allows the reduction of dyskinesia and a better mobility.

These improvements positively impact on activities of daily living and consequently on emotional well-being. DBS also alleviates the disability in patients with motor complications secondary to L-DOPA[4].

Until 1990, the surgical insertion of the electrodes was still very limited. However, this procedure became very safe with the microrecording. The microrecording is very important to reduce the discrepancy between the real anatomical path and the final placement of the electrode in the encephalic site of choice. Portions often used by neurosurgeons are the dorsal and dorsolateral portions of the STN. The DBS technique itself has a great advantage, which is reversibility. If the results are not demonstrated with the expected benefit, the electrodes can be deactivated, without any risk to the patients and with a return to the pre-operative condition[5,6].

Modern DBS for PD was introduced over 20 years ago. The surgical technique provided many therapeutic benefits for PD patients, but our understanding of the nuances of this procedure continues to improve. This review summarizes the main advances in DBS surgical technique in PD patients and our perspective for the future of the procedure.

METHODS AND RESULTS

We conducted a literature review on reliable databases (PubMed/MEDLINE, Scielo/LILACS and UptoDate) between the years 1960-2018. The selection considered the most relevant articles unsystematically.

The key terms used were “deep brain stimuation”, “previous pallidotomy”, “microrecording”, and “Parkinson disease”. A total of 64 papers were included for this narrative review.

DISCUSSION

Pharmacological Therapy for PD

L-DOPA is considered the gold standard for treating PD motor symptoms, yet tremor response to L-DOPA is highly variable among PD patients throughout the disease course. Although Parkinsonian tremor initially responds to dopaminergic agents in a majority of patients, it may become resistant to medications as PD progresses. Tremor control often comes at the expense of requiring increasing doses of medications[7].

In treatment with L-DOPA, patients typically experience a response to the early stages. However, the effect of L-DOPA begins to wear off approximately four hours after each dose, leaving patients anticipating the need for their next dose. This phenomenon has been explained by the observation that dopamine nerve terminals are able to store and release dopamine early in the course of disease. With the increasing degeneration of dopamine terminals, the concentration of dopamine in the basal ganglia is much more dependent upon plasma L-DOPA levels. Plasma levels may fluctuate erratically because of the 90-minute half-life of L-DOPA and the frequently unpredictable intestinal absorption of this medication[7].

The treatment consistency becomes difficult to maintain due to the need for frequent adjustments to the medication regimen. The response duration to L-DOPA shortens over time, which leads to motor fluctuations that must be counteracted by higher and more frequent doses. In addition, cognitive stress both increases the intensity of PD-related tremor and reduces the tremor-attenuating effect of L-DOPA, which further complicates tremor management. Non-dopaminergic circuits may contribute to Parkinsonion tremor and constitute an additional therapeutic target for tremor. Other medications for managing tremor are less effective or associated with intolerable side effects[7].

Motor fluctuations are alterations between periods of being “on,” during which the patient enjoys a good response to medication, and being “off”, during which the patient experiences symptoms of the underlying Parkinsonism. Dyskinesia usually appears when the patient is “on”[7,8].

They may occasionally occur in the form of painful dystonias when the patient is “off”. It occurs especially in the morning on awakening. The dystonic intorsion of a foot or curling of the toes (usually on the side of greater parkinsonian involvement) occurs as a withdrawal reaction because of the long interval without medication overnight[7,8].

PD therapeutic management aims to extend L-DOPA benefit while minimizing motor complications. It includes, in selected cases, the implementation of drug infusion and surgical techniques. In milder forms of motor complications, these can often be controlled with manipulation of L-DOPA dose and the introduction of supplemental therapies such as catechol-O-methyl transferase inhibitors, monoamine oxidase B inhibitors, and dopamine agonists including apomorphine[9].

PD drugs act only on the symptoms of the PD and do not prevent its progression. There are pharmacological agents in different phases of study. These agents aim to improve the treatment of patients with PD. Among them, we mention the coenzyme Q10, antioxidants, anti-apoptotic agents, N-acetyl cysteine, edaravone, glutamate receptor antagonists and adenosine A2A receptor antagonists. There are other types of emerging treatments for PD, such as the use of microRNAs, stem cells and glial-derived neurotrophic factor, transglutaminases and vector gene therapy[10].

Previous Surgical Techniques for Parkinsonism

In the past, GPi ablation and thalamotomies have been widely used as effective and successful options for the treatment of PD motor disorders. Currently, STN-DBS is the preferred surgical treatment. However, despite the good results obtained with surgeries, they do not stop the progression of the disease. DBS has very great efficacy, but this is directly related to the distribution of the tremor, with DBS being more effective in the treatment of distal appendicular tremors[11].

Radiofrequency and radiosurgery pallidotomies were initially used to treat tremor symptoms alone. These types of lesional procedures have been used to some extent in PD patients who decline or are poor candidates for DBS. There has been increased interest in the use of focused ultrasound (FUS) thalamotomies for tremor as it does not require a craniotomy and physical brain penetration[11].

Successful FUS thalamotomy for essential tremor has led investigators to treat highly selected tremor-dominant PD patients with FUS thalamotomy when the tremor is disabling and FUS subthalamotomy when there is an asymmetric disease presentation. While being a therapy that does not require an implanted device and successive operations for battery changes, lesional procedures are not reversible and thus are primarily performed unilaterally, limiting its effectiveness in a bilateral disease process[11,12].

Systematization of the DBS Technique

The DBS technique was introduced in the 1990s and is widely accepted as an effective treatment technique for patients with PD motor symptoms. Until 1990, surgical insertion of the DBS electrodes was still very limited due to technical limitations. Currently, the procedure is very safe and has a great advantage: reversibility. If the results are not demonstrated with the expected benefit, the electrodes can be deactivated, without any risk to the patients and with a return to the preoperative condition[13].

Some of the mechanisms of action of the electrodes should be mentioned: blockade of sodium channels, blockade of synaptic depolarization, point release of GABA neurotransmitter and activation of local inhibitory neurons in the target nucleus[13].

An efficacious STN-DBS imposes a new activity pattern within brain circuits, favouring alpha- and gamma-like neuronal discharge. This stimulus restores the thalamocortical transmission pathway through axonal activation. In addition, stimulation via the dorsal contacts of the macro-electrode may affect cortical activation antidromically. However, basal ganglia (BG) modulation remains cardinal for "off" and "on" transition. It is revealed by cGMP increase occurring during STN-DBS in the substantia nigra pars reticulata and internal globus pallidus[13].

Stefani et al.[13] hypothesized that STN-DBS will improve long-term potentiation (LTP) in motor cortex in PD patients. Their findings suggest that STN-DBS together with dopaminergic medications can restore LTP-like plasticity in motor cortex in PD. Restoration of cortical plasticity may be one of the mechanisms of how STN-DBS produces clinical benefit.

It is possible that the STN-DBS restores striato-centric bidirectional plasticity, and whether non-neuronal cellular actions play a part (microglia and neurovascular factors). Future studies will assess whether extremely anticipated DBS or lesioning in selected patients are capable of providing neuroprotection to the synuclein-mediated alterations of synaptic efficiency[13].

Even though the target for DBS consists of gray matter structures, DBS predominantly activates the axons rather than cell bodies of white matter tracts near the deep nuclei, which is of great relevance[14]. The measures of white matter microstructural properties and their alterations in various regions of the brain have shed light on important aspects of PD-related pathological process using diffusion imaging[15].

In PD patients, two tracts, namely the subthalamo-ponto-cerebellar tract (SPCT) and the dentate-thalamic tract (DTT) were identified. Sweet et al.[16] used probabilistic tractography and showed that active contact positions in proximity to DTT are associated with tremor improvement during the stimulation. Vanegas-Arroyave et al.[17] studied the tractography patterns of STN-DBS. They used probabilistic tractography and showed that from STN the areas which are frequently connected with the clinically effective contacts included the thalamus, the brainstem and the superior frontal gyrus. The strength of connectivity to the superior frontal gyrus and thalamus correlated with the clinical effectiveness.

Possible Adverse Effects of DBS Technique

After initiation of electrode stimulation, some patients may exhibit adverse side effects. With the reprogramming of electrode frequency, unwanted effects tend to disappear. After initiation of stimulation, drug doses tend do decrease as well as the amplitude of electrode stimulation[18,19].

Some surgical complications can result from the implantation of the DBS electrodes, such as: intracranial hemorrhages, intracranial hematomas and infections. Within this, the overall incidence of surgical complications is 2% to 3% (morbidity in 1% of patients and mortality in approximately 0.4%)[20].

However, confusion, dysarthria and dysphonia (3.4%) are the most frequently reported surgical

complications in DBS, followed by cognitive and psychiatric disorders (2.5 and 1.5%, respectively). Other serious complications include intracerebral hemorrhage (1.3%) and visual field deficits (0.2%). Death (0.1%) rarely occurs (intracerebral hemorrhage was significantly associated to the use of recording microelectrodes)[21].

Selection of Eligible Patient and Preoperative Management

Patients should be made fully aware that DBS is not able to cure the disease but it is able to optimize the motor symptoms, henceforth, the quality of life. Second Muthuraman et al.[22], the detailed initial evaluation is needed preferably in a movement disorder center. This support determines whether the patient will benefit from DBS. Generally, PD patients with intermediate to advanced disease are the most selected for the DBS procedure. For this purpose, an experienced team of neurologists specialized in movement disorders, functional neurosurgeons, psychiatrists and psychologists with experience in movement disorders needs to be homogenized.

The diagnosis of idiopathic PD should be confirmed, as other Parkinson syndromes usually do not respond to DBS. According Muthuraman et al.[23], patient's current and past antiparkinsonian medication as well as the dosing schedule should be carefully reviewed. The response to dopaminergic medication should be (re) tested as the improvement of motor symptoms after the L-DOPA challenge is one of the very few known predictors of the clinical outcome after DBS. Muthuraman et al.[23] relates that there is an imperative need for the development of an objective and investigator-independent paradigm that can accurately denote the symptoms that could be targeted by DBS and the approximate improvement after the surgery.

Welter et al.[24] describe that several clinical parameters have been analyzed as possible predictors of the post-operative clinical outcome of STN-DBS but until now dopaminergic response has been the strongest prognostic factor of post-operative outcome. The UPDRS score of a patient is assessed in the morning after overnight (approximately 12 hours) withdrawal of L-DOPA and 20 to 60 minutes after the patient has ingested 1.5 times their normal morning L-DOPA dose. The best possible ON time is rated as ascertained by the patient and the examiner.

Although there is no fixed limit of improvement required after the dopaminergic challenge for a DBS candidate, motor improvement of at least 30% is an objective response criterion. Conventionally, DBS is only offered to the patients who fulfill this response criterion because only those symptoms which are improved by L-DOPA are expected to be improved by DBS[25].

Schüpbach et al.[26] showed that younger patients benefited more from the DBS. However, the reason why younger patients have better motor outcomes after DBS is not clear. One suggested hypothesis was that the older patients may have more comorbidities and less capacity for neuroplasticity. Probably the age of PD patient is a predictor factor of outcome after DBS procedure.

Other important clinical criterion for a positive DBS response is the cognitive status of the patient. The presence of significant cognitive impairment is considered a contraindication for STN-DBS. A recent study using magnetic resonance imaging (MRI) demonstrated that cortical thickness of the frontal lobe (paracentral area and superior frontal gyrus) predicted the clinical improvement after STN-DBS. Baltuch et al.[27] demonstrated in patients with cortical atrophy of these areas, that a higher stimulation voltage was needed for an optimal clinical response. For cognitive assessment one of the following tests are conventionally used: Mini Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), DemTect, Parkinson Neuropsychometric Dementia Assessment (PANDA) or Mini Mental Parkinson (MMP)[28].

Preoperative Mapping for Insertion of Electrodes

Imaging the specific DBS targets and basal ganglia circuitry has also become more sophisticated. MRI continues to increase in resolution, which improves targeting of specific regions of the intended structure (STN and GPi). With advances in tractography, it is also possible to be able to target output and input circuitry as opposed to only the nodes within the BG. Not only is diffusion tensor imaging feasible for surgical planning of movement disorders, psychiatric disorders and pain DBS, but it may also improve surgical outcome[29].

The advances in imaging techniques, such as functional MRI and magnetoencephalography, provide tools to better understand connectivity between regions of the brain as well as brain activity associated with electrical stimulation. This information potentially could help in determining better functional and anatomic targets for DBS[29].

Ricciardi et al.[30] proposed the use of MRI in 3 Tesla (T) for better visualization of the STN-DBS in order to reduce the time required for microrecording mapping. 3T-MRI can provide less morbidity to the patient and greater treatment efficacy.

Cheng et al.[31] compared the sequences in 1.5 T and 3 T, demonstrating an advantage in the

observation and analysis of the STN in 3T for patients with advanced PD.

A prospective study concluded that both the conventional methods of microrecording (conventional Zamorano Dujovny frames and the preoperative platforms with individual mapping) allow effective and safe neurosurgical procedures. There is a lesser time of surgery for individual microrecording platforms[32].

There are still some limitations in terms of effectivity, side-effects, and battery consumption in DBS. Not only pathological but also physiological neural activity can be suppressed whilst stimulating. Adaptive DBS (aDBS) is applied according to the level of pathological activity. This method might be advantageous. Initial studies of aDBS demonstrate effectiveness in PD[33].

Many stimulation parameters can be used in aDBS. There are two different approaches to the application of high frequency aDBS: a binary approach, with effective stimulation either on or off, and a scalar approach with stimulation voltage being varied up to and including therapeutic values. The stimulation voltage is not rapidly increased with the induction of paresthesia. This issue is particularly important with binary on-off stimulation, where it is managed by the incorporation of a ramping of stimulation onset and offset[33].

Preoperative mapping of the specific point of the BG to be stimulated is crucial for the DBS outcome. The best points of stimulus to STN occur in the dorsal and dorsolateral STN borders. Electrode contacts used for chronic DBS in PD are placed near the dorsal border of the nucleus, a highly cellular region. DBS may thus exert its effects by modulating these cells, hyperdirect projections from motor cortical areas, afferent and efferent fibers to the motor STN[34,35].

Clinical Improvement in PD Patients after DBS

DBS is an adjunctive therapy that provides excellent tremor control. Patients reflect dramatic improvement in their lives following DBS surgery due to reduction or abolition of tremor. Tremor before DBS surgery is described as pervasive and inescapable. PD patients experience intense psychological sequelae as a result of prolonged intractable tremor prior to surgery, including feelings of embarrassment and shame[5].

The DBS is more effective than the best pharmacological therapy in alleviating disability in patients with moderate or severe PD. The extent of benefit is similar for younger and older patients. However, adverse events tend to be higher in older patients. STN-DBS reduces motor disability and improves quality of life in patients with advanced PD who have severe L-DOPA-induced motor complications[5].

There are improvements in motor functions and quality of life for many patients with PD after surgery. Preoperative levels of catecholamines showed a significant correlation with postoperative motor scores and quality of life. Yamamoto et al.[36] suggest that higher levels of pre-operative catecholamine come into contact with better results after STN-DBS. According to Yamamoto et al.[36], catecholamine levels were not significantly reduced postoperatively in 11 patients despite a significant reduction in equivalent L-DOPA doses in treatment. In this study, some patients showed increased cerebrospinal levels of homovalinic acid.

Schuepbach et al.[37] analyzed the DBS and its benefit at an earlier stage of PD. DBS was superior to medical therapy with respect to motor disability ($P<0.001$), activities of daily living ($P<0.001$), L-DOPA-induced motor complications ($P<0.001$), and time with good mobility and no dyskinesia ($P=0.01$). STN-DBS was superior to medical therapy in patients with PD and early motor complications.

Odekerken et al.[38] suggest that STN could be the preferred target for DBS in patients with advanced PD. There is no large difference in neuropsychological outcome between GPi-DBS and STN-DBS after 12 months[33,39].

There have been studies demonstrating the long-term efficacy of DBS for PD. The United States Veterans Affairs Cooperative study followed patients for 2 years, and demonstrated sustained symptom improvement and clinical efficacy for both STN-DBS and GPi-DBS[40].

Stable improvement in motor symptoms, improved quality of life measures, and decrease in L-DOPA equivalent daily dose have been reported at 4 years (STN), 5-6 years (STN and GPi), 6-9 years (STN), and 10 years (STN)[41-44].

Recent studies demonstrate the benefits of STN-DBS in patients with PD[45]. One meta-analysis assessed the long-term efficacy of DBS of the STN and GPi for Parkinson disease (PD). According to Peng et al.[46], STN-DBS and GPi-DBS improve motor function and activities of daily living for PD. Differences in the long-term efficacy for PD on motor symptoms were not observed. Other meta-analysis demonstrated that while there was similar individual efficacy of STN-DBS and L-DOPA, their combined effect on motor severity was additive within and beyond 5 years of follow-up[47].

Xie et al.[48] examined the impacts on individual motor subtypes (tremor, rigidity, and gait) between STN-DBS and GPi-DBS. They described no difference in the motor improvement of these patients. Therefore, responsiveness to both STN and GPi-DBS was similar among different PD motor subtypes. Compared to the GPi-DBS, STN-DBS

was more effective for reduction in medication. The study reported by Xu et al.[49] indicated that during the off-medication state, the STN-DBS might be superior to GPi-DBS in improving the motor function and activities of daily living for PD patients. But this study evaluated the short-term efficacy of STN-DBS and GPi-DBS.

The study reported by Odekerken et al.[50] showed more reoperations after GPi-DBS and a significant difference was observed. The electrode position of the initial surgery was considered optimal, and the need for reoperations from GPi-DBS to STN-DBS owing to waning effect. Volkmann et al.[51] also described 4 patients with good initial response to GPi-DBS but waning effect that required conversion to STN-DBS. This potential adverse event requires additional research.

Post-operative Long-term Care Management

Starting the DBS programming sessions a few weeks after the implantation allows time for reducing the microlesioning effect. Mascia MM describes that the stimulation based on constant current are applied in severe cases. It makes the stimulation intensity independent of the impedance[52].

To start the stimulation, the neurologist or neurosurgeon performs a primary testing, checking the clinical effects and the therapeutic window for each of the contacts and the range causing no side effects at each electrode contact, keeping the pulse and frequency constant. The contact with the best clinical benefit/side effects ratio is then activated on both sides. The medication therapy is then adapted to the stimulation, the most common being the first L-DOPA monotherapy[53].

The reduction of the L-DOPA needs a cautious approach to reach the threshold for best motor outcome with no troublesome dyskinesia. If the L-DOPA dose is insufficiently reduced, patients might develop side effects like dyskinesia or choreiform hyperkinetic movements, impulsivity and mania. However, reducing L-DOPA too much and too quickly might lead to apathy, depression or anhedonia[54].

Allert et al.[55] suggest that patients need specialized neuro-rehabilitation after DBS implantation. Before selecting a proper setting of post-surgical rehabilitation, the individual needs and goals for rehabilitation have to be defined for each DBS patient individually. The goal-specific therapy could be physiotherapy, Lee Silverman Voice Treatment (LSVT-BIG) therapy, speech therapy, occupational therapy, talk therapy, cognitive therapy or behavioral therapy depending upon the patient's need for best long-term clinical outcome.

Influence of Previous Ablative Surgery on DBS

There are studies showing that even in patients undergoing bilateral pallidotomy, DBS can bring benefits. Prior pallidotomy reduces the electrophysiological activity of the STN and therefore, its location during the operation may become more difficult. In patients who have performed previous unilateral pallidotomy, DBS is superior in relation to a second pallidotomy. Patients who underwent previous ablative surgery have lower benefits with DBS than those who did not perform prior surgery[56,57].

Pallidal stimulation and pallidotomy improve the symptoms of PD. However, it is not known which modality produces greater benefit in patients who have already undergone unilateral pallidotomy. It is also suggested that the original pallidal surgery provides a greater benefit than subsequent pallidal surgery. Pallidal stimulation produces greater symptom improvement than a second pallidotomy and subsequent surgery did not produce inferior results to the original pallidal surgery[58,59].

Patients who did not perform prior pallidotomy present more benefits in using DBS, evolving with better evaluations through of the UPDRS after implantation, which therefore places the prior pallidotomy as an important aspect to be considered in the indication of DBS[60-62].

One study included 22 patients who underwent STN-DBS. Khabarova et al.[63] described that eleven patients had undergone prior unilateral pallidotomy (n = 6) or VL/VIM thalamotomy (n = 5) while the other 11 patients had not. The primary outcome was the change from baseline in the motor subscore of the UPDRS-III 12 months after STN-DBS. Secondary outcomes included change in motor response complications (UPDRS-IV) and change in L-DOPA equivalent daily dose (LEDD).

Khabarova et al.[63] demonstrated that in the group with prior lesioning UPDRS-III improved by 45%, from 51.5 ± 9.0% (range, 35-65) to 26.5 ± 8.4 (range, 21-50) ($p < 0.01$) and UPDRS-IV by 75%, from 8.0 ± 2.01 (range, 5-11) to 2.1 ± 0.74 (range, 1-3) ($p < 0.01$). The group without prior lesioning UPDRS-III improved by 61%, from 74.2% ± 7.32 (range, 63-82) to 29.3 ± 5.99 (range, 20-42) ($p < 0.01$) and UPDRS-IV by 77%, from 9.1 ± 2.46 (range, 5-12) to 2.0 ± 1.1 (range, 1-4) ($p < 0.01$). Comparing the two groups (with and without lesioning) no significant differences were found either in UPDRS-III ($p > 0.05$) or UPDRS-IV scores ($p > 0.05$) at 12 months post-DBS.

Khabarova et al.[63] demonstrated that the LEDD was reduced by 51.4%, from 1008.2 ± 346.4 to 490.0 ± 194.3 in those with prior surgery ($p < 0.01$) and by 55.0%, from 963.4 ± 96.2 to 433.3 ± 160.2 in those without ($p < 0.01$). UPDRS-III improved by 51.8%, from 53.7 ± 4.6 (range, 50-62) to 25.0 ± 3.8

(range, 21-31) in those with prior pallidotomy ($p < 0.01$), and by 37.5%, from 48.8 ± 12.6 (range, 35-65) to 29.8 ± 13.6 (range, 22-50) in those with prior thalamotomy ($p < 0.01$). This study indicates that bilateral STN-DBS is effective and can be used in patients with PD with prior unilateral stereotactic destructive operations on subcortical structures.

In patients who performed a previous unilateral pallidotomy, the DBS is superior in relation to a second pallidotomy. There is still no consensus on the influence of unilateral pallidotomy on the electrophysiological characteristics of the contralateral STN. STN may be intact or intermediate to the ipsilateral side to the pallidotomy and a brain without previous palidotomy[63].

Ablative Techniques versus DBS Technique in The World

Of the neurosurgeons still using ablation on the subthalamic nucleus as the surgical treatment of PD, approximately 15% use more than one ablative technique. The vast majority of neurosurgeons worldwide (more than 85%) prefer the DBS technique as the best strategy for surgical treatment of Parkinsonism in the PD[64].

In the last two decades, few studies on DBS and PD have been published. Most of the data are concentrated in specific subgroups of neurosurgeons, mainly from North America and Europe. It should be noted that the overall financing for the surgical treatment of PD is guaranteed by public investment in many countries, but there are still many barriers in others countries, like Brazil[64].

CONCLUSION

Motor complications can be disabling for PD patients. Their management is complex and requires experienced assessment to provide the best treatment choice. Currently available therapies include drug manipulation and surgery. New approaches are being investigated, and the number of treatment options is increasing. In general, the best results are achieved with timely referral to tertiary centers that provide appropriate patient screening and selection as well as a multidisciplinary approach.

The PD patients should be properly evaluated by a multidisciplinary team of movement disorder specialists that would ideally include neurologists, neurosurgeons, neurophysiologists, psychiatrists, neuropsychologists, nurse practitioners, and physical therapists. This would also require the ability to provide monitoring of efficacy to assess the benefit of the various therapies, and specifically to make the decision to move from conventional pharmacologic treatment to more invasive infusion or surgical treatments.

Modern DBS for PD was introduced over 20 years ago, but our understanding of the nuances of this procedure continues to improve. Despite remarkable success in controlling the primary motor symptoms of PD, a modeling platform that would predict whether STN or GPi stimulation is most likely to provide optimal benefit for a given patient does not exist, nor have the mechanisms for adverse non-motor symptoms been defined.

Nonetheless, expansion of patient selection criteria to include younger and older patients and the advent of real-time imaging-confirmed DBS electrode placement are making this life-changing treatment highly effective and available to greater numbers of movement disorder patients. Future challenges in advancing DBS in PD involve developing a better understanding of the intrinsic circuitry of each target, which can only come from studies of basal ganglia physiology. One of the ultimate goals to be achieved with DBS is to maximize efficacy while minimizing side effects to PD patients.

Conflicts of Interest

The authors declare no conflicts of interest.

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