Surgical Management of Parkinson's Disease: Update and Review

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Summary

Although medical therapy is still the mainstay of treatment for Parkinson's disease, the development of surgical precision and decreased morbidity have made stereotactic lesioning and deep brain stimulation more popular. Neurosurgical ablations include pallidotomy, thalamotomy, and, more recently, subthalamotomy. Because of concern over the high risk of side-effects resulting from bilateral ablative procedure, alternative approaches have been explored. With improved deep brain stimulation (DBS) technology, DBS has been successfully applied in the internal globus pallidus, ventral intermediate nucleus and subthalamic nucleus for Parkinson's disease.

In addition, recent surgical approaches including biological neurorestorative technologies - surgical therapies with transplantation, gene therapy, and growth factor are all being discussed in this review. Although a great deal of work remains to be done for researchers, advances in surgical therapies for the treatment of Parkinson's disease are moving forward at an unprecedented pace, and, not surprisingly, would give PD patients more choices and hope.

Introduction

Parkinson's disease, which is characterized by a clinical triad of akinesia, rigidity and tremor marked by degeneration of dopaminergic

neurons in the substantia nigra pars compacta, is an age-related neurodegenerative disorder and can result in significant disability and morbidity. In the early stage of the disease most symptoms can be well controlled by L-DOPA, but with its continuous usage multiple motor side effects develop, which include the end-of-dose 'wearing off' phenomenon, Levodopa-induced-dyskinesia (LID), "on-off" fluctuation, involuntary movements, neuropsychiatric phenomena, and sensory symptoms, etc.¹⁻⁴. Since medical therapy fails to provide good, long-lasting relief of symptoms, interest in the surgical treatment of PD has been rekindled.

The surgical treatment of PD is not a new idea; as early as in 1912 surgical procedures were applied to relieve the symptoms of PD^{5,6}. Pallidotomy and thalamotomy were introduced as surgical therapies for PD in the 1940s and 1950s⁷. With the introduction of L-dopa in the 1960s and the high morbidity and mortality associated with surgical treatment, surgical treatments of PD became obsolete and were almost supplanted by medical treatment. Within a decade, however, the limitations of L-dopa became apparent.

At the same time, advances in stereotactic neurosurgical procedures provided surgeons with more effective methods of treating PD with lower morbidity and mortality than in earlier eras. With the rediscovery of the potential benefits of surgery, ablative neurosurgical procedures of PD have experienced a renaissance

since the 1980s. In this paper, surgical procedures in the post-levodopa era are critically reviewed.

Neurophysiology relevant to treatment of Parkinson's disease

The rebirth of PD surgery during the past decade has been facilitated by advances in our understanding of the basic anatomy and physiology of the basal ganglia and motor systems, as well as the pathophysiology of PD. In the parkinsonian state, the natural balance within the motor loop is lost owing to the depletion of dopamine in the striatum. Both the direct and indirect pathways operate through the GPi/SNr output nuclei and their influence is inhibitory on the thalamus.

The loss of dopamine leads to increased activity in the output nuclei, which in turn leads to underactivation of motor cortical areas, resulting in a reduction in movement observed in patients as the hypokinetic symptoms of PD (rigidity and bradykinesia)^{3,4,8,9}.

This model of basal ganglia activity accounts generally for the clinical effects of pallidal interventions, such as pallidotomy, that are aimed at reducing the abnormal GPi activity. Attenuation of GPi overactivity restores more normal thalamocortical and brainstem activity and alleviates hypokinetic symptoms and tremor. The model also predicts that therapies directed at reducing the overactivity of STN might have even greater clinical effects than therapy directed at GPi because STN intervention restores more normal activity in both GPi and SNr, whereas therapy directed toward GPi does not correct abnormal activity in SNr^{3,4,8,9}. This prediction has been borne out by preliminary clinical studies.

Ablative surgery

Before the introduction of levodopa, the treatment of severe PD by selective destruction of basal ganglia was the only option available. There is no comprehensive theory behind this approach; it was discovered by chance, and targeting of specific areas of the brain is still mostly empirical¹⁰. Although ablative treatments, as well as DBS, are not curative, their success rate in improving PD symptoms is usually reported in the range of 40 to 90%, depending on specific treatment and observation period.

Thalamotomy

In the thalamus, the ventral intermediate nucleus is the primary region targeted for the relief of the tremor. Lesions in the ventral intermediate nucleus are highly effective in alleviating parkinsonian tremor in more than 85% of patients¹¹. If extended anteriorly to include the ventral oralis posterior, and possibly portions of the ventral oralis anterior, rigidity and dopa-induced dyskinesia also improve¹².

Thalamotomy generally does not improve bradykinesia or akinesia and may exacerbate speech and gait disorders in some patients^{13,14}. In addition, bilateral thalamotomy can relieve bilateral parkinsonian disease, but results in a prohibitively high rate of cognitive and speech problems^{13,15}, which prevent the use of this procedure for most patients with Parkinson's disease. Given the success of pallidotomy and DBS of the subthalamic nucleus and internal globus pallidus in improving all the cardinal motor symptoms of Parkinson's disease and the lower incidence of side-effects with DBS, thalamotomy is generally not recommended.

Pallidotomy

Pallidotomy, a widely accepted surgical treatment for PD, improves tremor, rigidity, and bradykinesia in most patients¹⁶⁻²⁵. As measured by a standardized assessment tool, the Unified Parkinson's Disease Rating Scale (UPDRS)²⁶, pallidotomy improves motor scores (measured while patients are off medications) from 14%²² to 69%¹⁷. Levodopa-induced dyskinesias, which occur while patients are on medications, improve significantly with reductions (based on the UPDRS dyskinesia scale) ranging from 49%¹⁹ to 73%²⁴. UPDRS Activities of Daily Living scores improve 30-50%^{16,20}. Most clinical benefit from pallidotomy is seen on the side of the body contralateral to the procedure. Ipsilateral and axial (e.g. postural instability) symptoms can improve, but these improvements are not maintained consistently past one year^{16,18,20,27,28}. Medication requirements generally do not change after pallidotomy^{16,20,27,28}.

Serious complications from unilateral pallidotomy are not common (generally in the range of 2-8%)^{9,27,29}. Complications that do occur tend to be mild and are frequently transient. Complications include visual impairment^{7,9,30}, facial paresis, hemiparesis^{7,9,29,31}, and

changes in speech, voice volume and memory. Changes in neuropsychological status have been reported but are not a consistent finding^{16,28,32-34}.

Although the primary clinical benefit of pallidotomy is contralateral to the surgical site, some patients improve sufficiently after unilateral pallidotomy to make bilateral pallidotomy not necessary. For others, bilateral pallidotomy can provide improvement in symptoms beyond that provided by unilateral pallidotomy^{27,35-37}. Most patients undergoing bilateral pallidotomy are pleased with the outcome, but the risk of complications is substantially greater when the procedure is performed bilaterally^{33,38,39}. In particular, bilateral pallidotomy may cause dysfunction of speech (hypophonia and dysarthria), swallowing (drooling)^{33,38}, balance and memory in as many as 50% of patients. Concerned about the incidence of complications following bilateral pallidotomy, some experts recommend against the procedure except for limited indications^{9,27,38,40}. Bilateral DBS (or contralateral DBS for patients who have undergone a unilateral pallidotomy) may provide a safe alternative to bilateral pallidotomy.

Subthalamotomy

Whereas many studies reported that pallidotomy or thalamotomy can effectively improve parkinsonian symptoms, few research groups have carried out subthalamic lesions studies. Because of the intractable hemiballism associated with lesions in the subthalamic nuclei, researchers were reluctant to explore this therapeutic approach.

After DBS of the subthalamic nucleus was successfully applied to the treatment of Parkinson's disease, a series of subthalamotomy case reports, as a cheaper alternative to DBS, have been reported in the past decade.

A study of up to 21 patients with unilateral subthalamic lesions has showed that UPDRS motor score in the 'off-medicine' was improved by 15-50% at two year follow-up⁴¹⁻⁴³. With bilateral subthalamotomy, Alvarez and colleagues reported 18 patients with 58% improvement in the off-medicine UPDRS motor score and a 63% improvement in the on-medicine score at two years⁴⁴. Up to half of the patients developed Huntington's chorea, but in most cases the symptom was mild, lasting from a few hours to five days^{41,42}.

One group reported that one patient developed refractory chorea eventually leading to fatal aspiration pneumonia. However, others have found that postoperative chorea can be easily ameliorated by an ipsilateral pallidotomy⁴¹ or thalamotomy of the ventral intermediate nucleus and ventral oralis posterior⁴⁵.

These promising results suggested that compared with pallidotomy or DBS of the subthalamic nucleus or GPi, subthalamotomy can also be safely carried out and have beneficial effects. Although the hazard of hemichorea exists, its incidence is not as high as previously thought. Thus far, side-effects of speech and cognitive functions resulting from bilateral subthalamotomy seem to be fewer those that of bilateral pallidotomy or thalamotomy, and at the same time, drug intake can be reduced.

Deep brain stimulation, DBS

Benabid et Al.⁴⁶ were the first to propose that chronic high-frequency deep brain stimulation (DBS) could simulate the effects of a lesion and avoid the need to make a destructive brain lesion and might be a useful treatment in PD. They proposed that chronic stimulation could be accomplished by connecting an electrode implanted into a specific brain target to a programmable stimulator. Optimal stimulation parameters could be determined by varying the electrode configuration (each electrode has four individual contact sites), and the stimulation voltage, pulse width, and frequency. DBS had previously been employed as a therapy for intractable pain and dyskinesia^{47,48} and was shown to be well tolerated. The principal advantage of DBS is its capacity to provide functional benefits without the necessity of creating a destructive brain lesion, thereby avoiding adverse events caused by damage to neighboring structures. This is a particular advantage if bilateral procedures need to be performed. It also permits targeting regions in the brain that one might be unwilling to lesion such as the subthalamic nucleus (STN) or the GPi bilaterally. Other advantages of DBS include the potential to adjust the stimulator at any time after surgery in order to maximize benefits and minimize adversity.

Further, the procedure does not mitigate against the introduction of a more effective therapy in the future that requires the integrity of the basal ganglia system.

Ventralis intermedius nucleus, VIM

DBS for PD was first tested in the VIM nucleus of the thalamus in patients with tremor predominant symptoms^{49,50}. DBS of the VIM nucleus was initially investigated in patients who had previously undergone a thalamotomy in order to diminish the risks associated with bilateral thalamic lesions⁵¹. DBS of the VIM has now been shown to dramatically ameliorate contralateral tremor⁵², and these results have been confirmed in a double-blind crossover study⁵³. A randomized trial demonstrated that DBS-VIM provides benefits comparable to thalamotomy with fewer adverse events⁵⁴. Tremor reduction is generally observed one to three seconds after the stimulator is turned on and the effect is lost within seconds after the stimulator is turned off. Benefits have been observed to persist for as long as ten years and benefit continues to be lost when stimulation is discontinued.

Unfortunately, the benefits of DBS-VIM do not extend to the more disabling parkinsonian features such as rigidity, bradykinesia and gait dysfunction. For this reason, interest has shifted to stimulation of the GPi and subthalamic nucleus (STN) as primary targets in PD based on preclinical and clinical evidence indicated that stimulation of these targets has a greater possibility of improving the entire constellation of parkinsonian motor dysfunction.

The most common complication of DBS-VIM for Parkinson's disease tremor is worsening dysarthria, which occurs in about 20% of patients. Tremor is more common with bilateral stimulation and can be decreased with adjustment of stimulation parameters⁴⁹. This rate of complications is lower than the 30%~50% incidence of speech difficulties in patients with bilateral thalamotomy. The major advantage to Vim stimulation is that unlike thalamotomy, the side-effects resulting from stimulation are reversible^{55,56}. However, the lack of reliable efficacy on other motor symptoms has limited the use of DBS-VIM for Parkinson's disease.

Globus Pallidus Internus, GPi

The only large, prospective, double-blind study of bilateral DBS of the internal globus pallidus was a multicentre study that reported a 37% improvement in "off-medicine" UPDRS motor subscore in 38 patients at three months⁵⁷.

Although this study enrolled patients for both bilateral internal-globus-pallidus DBS and subthalamic-nucleus DBS, patients had not been randomized to stimulation site. This study was designed to show safety and efficacy and not to compare the two modalities.

The only randomised, blinded comparison of DBS of these two targets was small (ten patients) and did not show a significant difference between the sites: internal-globus-pallidus DBS caused a 39% improvement at one year in four patients⁵⁸. Other bilateral internal globus pallidus case analyses showed consistently positive results with improvement in "off" motor subscore up to 56%. Studies of bilateral stimulation of the internal globus pallidus in patients of followed up for two years or longer have shown stable benefit. The results of one study of the bilateral globus pallidus DBS in 11 patients followed up for up to five years showed that dyskinesias remained significantly reduced until the last assessment, but initial improvement of "off"-period motor symptoms and fluctuations was not sustained and gradually declined⁵⁹. Whether or not this study is representative of the long-term effect of DBS of the internal globus pallidus requires further study in more patients. In contrast to thalamotomy or Vim DBS, GPi DBS has reliably alleviated all cardinal motor symptoms of Parkinson's disease including akinesia, bradykinesia, rigidity, tremor and gait^{39,57,58,60-67}. DBS of GPi improves "off" dystonia^{68,69} and, like pallidotomy, has a strong, direct, suppressing effect on levodopa-induced dyskinesias^{39,58,65,70-72}. Internal-globus-pallidus stimulation also improves postural instability and gait^{60,63,73-75}. These changes were more noticeable in patients with bilateral rather than unilateral stimulation. In addition, "on" time is substantially increased: the 38 patients in the DBS for Parkinson's disease improved their percentage of "on" time from 28% to 64%⁵⁷.

Complications directly related to GPi stimulation are moderate, and are generally reduced or eliminated with adjustment of stimulation parameters. There are few reports of adverse effects on speech, mood and cognition, and case reports of mania⁷⁶, apathy⁷⁷ and mild decline in lexical verbal memory³⁹. Of the studies of detailed neuropsychological testing, most have shown that no overall change, with minimum subclinical changes occurring in some patients^{78,79}.

Subthalamus Nucleus, STN

DBS of the subthalamic nucleus, like that of the internal globus pallidus, improves all cardinal motor symptoms of Parkinson's disease. No randomised, blind clinical experiments have showed the superiority of one method over the other. However, DBS of the subthalamic nucleus is generally preferred and is done more than that of the internal globus pallidus. Study of DBS for Parkinson's disease showed that in "off-medicine" UPDRS motor subscore, improvement in bilateral stimulation of subthalamic nucleus is slightly greater than that of bilateral stimulation of the internal globus pallidus, 49% and 37% respectively⁵⁷. But this study was not blinded and did not randomly assign patients by sites. As such, it is difficult to compare the results from the two sites. These results and those of other studies of stimulations of the subthalamic nucleus have been consistently robust with most studies showing 45-55% improvement and some showing as high as 60-70% improvement in "off" medicine motor subscore^{57,58,60-62,80-82}. Study of 42 patients followed up for five years showed that improvement seems to be stable with continued efficacy and a 54% improvement in "off" motor score⁸⁰. "On" time is also significantly increased from baseline 27% to 74% at three months⁵⁷. Bilateral stimulation of STN may produce dramatic beneficial effects on midline symptoms such as gait, posture and balance⁶⁰.

Although intake of antiparkinsonian drugs can be substantially decreased with subthalamus DBS, drug adjustment may be more difficult than that with stimulation of the internal globus pallidus^{81,83-85}. Some centres substantially decrease drugs after surgery; there are now reports that patients do not tolerate this and experience significant mood side-effects. If done properly - titrating stimulation variables up as treatment is reduced - patients tolerate these adjustments well and continue to show significant improvement in postoperative motor scores⁸¹.

In addition to stimulation-induced dyskinesia, there are more reports of mood, behavioural, and cognitive side-effects associated with subthalamic-nucleus stimulation than with internal-globus-pallidus stimulation. This may be due to higher subthalamic nucleus implantation rates and therefore there are more reports of side-effects. However, the unique anatomic

characteristics also cause this effect - its small size necessitates implantation of a DBS lead in regions near non-motor portions, and its vicinity to important neighbouring structures. Inadvertent current spread into non-motor portions of the STN and adjacent structures may affect cognition and behaviour by modulation of frontal and limbic function. DBS of the subthalamic nucleus may worsen the cognitive function of some patients, especially older patients⁸⁶ and those with preoperative cognitive decline⁸⁷. By contrast, young and non-demented patients show no significant cognitive change⁸⁸. Limbic circuits have strong connections with the medial subthalamic nucleus, and not surprisingly, stimulation can cause apathy, depression or mania^{62,86,89-93}. Depression and apathy may also occur because of a sudden reduction of levodopa and hence patients may show an improvement with increasing dopaminergic treatment⁹⁴. DBS of the subthalamic nucleus, especially with stimulation in the left side, also produces depression^{90,95}; whereas right side stimulation can develop mirthful laughter⁹⁶. Most side-effects associated with stimulation of the STN can be reduced with adjustment of stimulation parameters. However, mood and cognition changes can be more occult, and may not be immediately noted.

Cell Transplantation

The methods described above so far aim at altering the physical manifestations of the disease without affecting its natural history. Cell transplantation, on the other hand, is an alternative approach to treat PD by replacing the dopaminergic neurones within the basal ganglion, and thereby reversing or compensating for the ongoing neurodegenerative process. Although initial attempts to replace lost neurons in PD patients by transplantation date back almost 20 years, this approach is still in an experimental, preliminary stage. The first problem to be resolved is the origin of the material to be transplanted. Three major sources of dopamine-producing cells are being considered.

Human Fetal Neural Cells

One type of transplantation is dopamine-producing neurons or their precursors from human fetal tissue, most notably human embryonic dopaminergic nigral grafts.

There have been sporadic case reports of fetal neural transplantation for Parkinson's disease over the years with Freed and colleagues publishing the first placebo-controlled trial⁹⁷. Although uptake of fluorodopa increased on PET scan, clinical improvement did not always correlate and was more profound in younger patients. In addition, 15% of the patients demonstrated dyskinesias similar to those seen on levodopa.

Subsequent discussions have arisen regarding the severity of dyskinesias seen after neural transplantation. Hagell et Al⁹⁸ reviewed 14 patients who received fetal transplantation with up to 11 years of follow-up. They found that eight of these patients had mild dyskinesias that caused no distress to the patient. Of the remaining six patients with more severe dyskinesias, there was only one patient with a clinical therapeutic problem. However, these patients are difficult to compare with one another because they underwent transplantation under different conditions. Ma et Al⁹⁹, in a study with PET using (18F) fluorodopa, concluded that uptake was increased significantly in patients with dyskinesias after transplants as compared with those without dyskinesias, and these increases were predominantly in two zones within the putamen. These findings suggest that more targeted transplantation is necessary and that there exists a therapeutic window in which increasing dopamine with transplantation does not cause dyskinesia. Despite these issues, the authors concluded that this is not a sufficient reason to discontinue studies using fetal neural transplantation. Double grafts in the putamen and substantia nigra are reportedly safe and have shown improvement in UPDRS in three patients¹⁰⁰.

XenoTransplantation

The difficulties with using human foetal tissue have led to the search for alternative sources of tissue, including porcine neural cells. However, there are fundamental problems with using such tissue, including risks of infection and issues of immune rejection^{101,102}. Neither of these problems has been resolved experimentally and so it is not surprising that the clinical results to date have been largely disappointing, with some clinical improvement but no significant dopaminergic cell survival at post-mortem or on ¹⁸F-dopa PET scans¹⁰³⁻¹⁰⁵.

Stem Cells

The question of whether fetal transplantation could provide adequate numbers of dopaminergic cells has led researchers to look to embryonic stem cells for the treatment of Parkinson's disease. Although animal studies have shown that survival of these cells is four times higher than that of fetal cells, only 22% of grafted cells survived and only a small fraction of those expressed dopamine¹⁰⁶. Kim and coworkers¹⁰⁷ expressed the Nurr 1 protein in embryonic stem cells prior to transplanting them into rats. Nurr 1 plays a role in differentiation of mid-brain precursors into dopamine-producing neurons, and may influence cell survival. The animals exhibited improvement in parkinsonian symptoms and in electrophysiologic properties¹⁰⁸. Other methods of inducing dopamine production from stem cells have been used with less or similar success¹⁰⁶. More recent studies suggest that stem cells can potentially develop dopamine phenotypes^{109,110}.

Embryonic stem cells can also be engineered to deliver other drugs and growth factors. Temporary increases in survival of co-grafted primary dopamine neurons were seen with stem cells engineered with GDNF¹¹¹. GDNF expressing neural stem cells still differentiated into astrocytes, neurons, or oligodendrocytes. Even after differentiating, they continued to express GDNF. They also prevented degeneration of dopamine neurons after 6-hydroxydopamine injections and reduced apomorphine- and amphetamine-induced turning behavior when compared with controls¹¹². Their advantage over viral delivery is that the neurons are not genetically changed and there is no chance of mutagenesis¹⁰⁶. Akerud et Al¹¹³ over-expressed persephin, a member of the GDNF family, in neural stem cells. They demonstrated *in vivo* findings similar to those with GDNF when injected into mouse striatum.

Stem cells currently are an extremely attractive but controversial therapy. Social issues continue to influence the pace of scientific progress and probably will limit the supply of available tissue if renewable sources of functional cells are not found. Several scientific hurdles also remain. Embryonic stem cells may not be immunologically compatible with most patients, and they could cause teratomas if tight control over differentiation and cell proliferation is not achieved. Our understanding of the

rules and limits to integration of differentiated cells into neural circuits is also in its infancy. A complete understanding will be necessary if we are to realize fully the potential of stem cells. Nonetheless, the active interest and substantial recent progress in this area sustain the enthusiastic hope that this approach could eventually achieve the ultimate goal of repairing the damaged brain.

Growth Factor and Gene Therapy

In addition, other researchers propose the use of neural trophic factors for the treatment of Parkinson's disease. Neural trophic factors have been used as a method of promoting the restoration and maintenance of degenerating dopaminergic cells^{114,115}. A large, multicentre, double-blind placebo controlled trial of intraventricular infusion of gail-cell-derived neurotrophic factor showed no benefit at eight months¹¹⁵. After these disappointing results, investigators proposed direct infusion of gail-cell-derived neurotrophic factor into putamen. The open-label, phase I clinical study showed a 39% improvement in the "off" UPDRS motor score in patients receiving up to 43.2 µg/putamen/day of gail-cell-derived neurotrophic factor¹¹⁴. Gene therapy has been tried to introduce GDNF to basal ganglia for the treatment of Parkinsonian motor symptoms. In an MPTP monkey model of Parkinson's disease, production of gail-cell-derived neurotrophic factor in striatum and substantia nigra was increased and associated with improvement of parkinsonian symptoms¹¹⁶. Whether the use of gene

therapy of infusion to introduce trophic factors into the nervous system will prove to be effective is unknown.

Another method using gene therapy has been started to deliver glutamic acid decarboxylase into subthalamic-nucleus glutamatergic cells with the aim of promoting GABA production in these cells, thus changing the action of these neurons from excitatory to inhibitory¹¹⁷ and reducing the excessive output from the subthalamic nucleus proposed to underline the development of many of the motor signs of Parkinson's disease.

Conclusions

For a select patient population, stereotactic ablation and DBS have significant roles to play in the treatment of Parkinson's disease. The use of thalamotomy and thalamic DBS should be limited to those patients with mainly drug resistant tremor. Stimulation of the globus pallidus has been shown to be of benefit, but it has been largely supplanted by bilateral STN DBS. In patients who respond to L-dopa but have intolerable adverse effects, STN DBS can decrease medication dosage and improve function status. Gene therapy, direct drug infusion, and fetal cell transplantation have all been or currently are in clinical trials, so that scientifically advanced treatments are no longer exclusively theoretical.

Continued developments in these areas and in stem cell research will probably alter surgical practice for Parkinson's disease patients within the foreseeable future.

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