Current surgical treatment of Parkinson's disease

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ABSTRACT

There has been a renaissance in the surgical management of Parkinson's disease. This has been due to long-term effects of levodopa and a better understanding of the basal ganglia and its circuitry. Ablative surgery and neurostimulation are the only realistic surgical options at present. Although surgical treatments, such as ablation and stimulation are effective, they are not useful for stopping the progression or restoring the system. Neural transplantation helps restore the system by using a number of techniques. Targets mostly used are in the thalamus, globus pallidus and subthalamic nucleus. A number of factors must be considered including patient's age, disability and his wishes. Globus pallidus stimulation might be preferable for patients who suffer from dyskinesia as a major source of disability. Pallidotomy might be appropriate in cases where frequent stimulator adjustments are impractical. Subthalamic nucleus stimulation is more suitable for patients with significant off periods and in younger patients in whom it may be desirable to maintain intact circuitry. Fetal neural transplantation, stem cell transplantation, xenotransplantation, adrenal medullary transplantation and transplantation of genetically engineered cells are at various stages of development and research. Ethical issues surrounding these process are likely to arouse strong emotions and have to be carefully considered.

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In the recent years there has been renewed interest in the surgical management of Parkinson's Disease (PD).[1] This is due to the better understanding of the basal ganglia circuitry and continuing evolution of neurosurgical techniques.[2] The other reason for looking at the surgical option emanates from the fact that the positive effects of levodopa tapers off within 5-15 years and the patient is left with few options for treatment. In particular, patients experience severe levodopa induced dyskinesia during "on periods" and profound tremor, rigidity and akinesis during "off periods". It becomes increasingly difficult to manage balancing control of PD symptoms with adverse effects of medications. The 3 major surgical treatments for PD patients are ablative procedure for example, thalamotomy and pallidotomy, electrophysiological, for example deep brain stimulation and restorative for example cell transplantation.[3] Cell transplantation has not met the expectations as yet. Deep brain stimulation is gaining ground and currently seems to be the most efficient flexible and safe procedure.[4]

Indications for surgery. Patients considered for surgery should have disabling idiopathic PD with a documented response to dopamine replacement therapy. In some patients with severe Parkinsonian signs the available pharmacologic tools do not provide sufficient control. Typically such patients have severe dyskinesia when mobile ("on") and suffer unbearable immobility when "off". Although surgery and drugs provide similar effects, the difference is that surgery may improve so dramatically the "off" state as to eradicate motor fluctuation, and it may thus allow patients to enjoy relatively constant and complete autonomy. In addition, dyskinesia is much improved. Severe levodopa resistant tremors, which have initially been controlled with levodopa or apomorphine but later

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becomes resistant on long-term basis is another indication. Young and frequently very active persons do not tolerate levodopa and other anti-parkinsonian drugs in a rare clinical situation. Contraindications to surgery include the "PD-Plus" syndromes, such as progressive supranuclear palsy and multi-system atrophy as these disorders are associated with neuronal loss in multiple areas and the standard neurosurgical procedure are often ineffective. Serious systemic illnesses and dementia are other contraindications to surgery.[5] Positive developments in the neurosurgical therapies for PD are the wide spread formation of movement disorder clinics and recognition of the need for a team approach combining various specialities, including neurology, neurosurgery, neurophysiology, neuropsychology and movement disorder nursing.

Surgical options. Ablative surgery and deep brain stimulation are the only realistic options for the neurosurgical management of PD at present. Ablative surgery and deep brain stimulation can be performed in the thalamus, the pallidum and the subthalamic nucleus. The safety and efficacy of unilateral pallidotomy is well established. Deep brain stimulation has a lower morbidity and is preferred for bilateral surgery. The subthalamic nucleus presently seems to be the most promising target in advanced stage PD.[6] The surgical techniques are similar for all targets. The surgical targets are identified using stereotactic magnetic resonance imaging or computed tomography, or both prior to surgery. The patient is then transferred to the operating theatre and the procedure is performed with the patient awake. A burr hole is made under local anaesthesia that allows the introduction of recording, lesioning and stimulating electrodes. Most centres use microelectrode recordings to precisely determine the location of the nuclei. Stimulation can also be used to delineate the target location. Once physiologic confirmation is completed, the lesion is generated or the DBS electrode is placed. If a stimulator is inserted the patient is given a general anesthetic after confirmation of the brain electrode placement, to allow infraclavicular pulse generator implantation.

Ablative treatments. Thalamic lesioning. Thalamotomy has been used in the management of PD for over 40 years. There is little disagreement that thalamic lesions, usually targeting the ventral intermediate nucleus (VIM) can markedly reduce tremor but have little effect on other parkinsonian symptoms. Generally, a good to marked effect on contralateral resting tremor is reported in 75-85% of patients.[7] A significant long term benefit (mean, 11-years) has been demonstrated in the only blinded analysis of response to thalamotomy performed to date. Complications are not rare including persistent paresthesia, dystonia, dysarthria and cognitive changes. The later 2 are more frequent following bilateral procedure.

Globus pallidus lesioning. Presently, unilateral posteroventral pallidotomy (PVP) is probably the most wide spread surgical procedure for the advanced stage PD.[7] It is the most widely used treatment of peak dose dyskinesia and for dystonia that occurs at the end of a dose. It may also improve bradykinesia and to a lesser extent contralateral tremor. Although short-term results of pallidotomy are well documented, data on long term results and on bilateral PVP are sparse. It is most effective in patients under the of age 70-years.[8] Axial symptoms such as speech; gait and freezing in most studies are not improved after unilateral PVP. This may be the main reason why levodopa is not reduced after PVP.[7] Recently the first randomised, single blind, multi centre trial of unilateral pallidotomy has been published confirming significant benefits in "off" period PD and levodopa induced dyskinesia (31% and 50% improvement).[9] In another recent report, long term results of pallidotomy in 20 patients were analyzed.[10] Some symptoms of the "on" periods stayed improved for 5-years and longer and the author concluded that for a subset of severely affected patients, pallidotomy remains the treatment of choice.

Subthalamic nucleus lesioning. Subthalamic nucleus lesioning (STN) is not a popular procedure in the humans with PD. There has been reluctance to lesion this area for fear of inducing disabling hemiballismus. There have been recent reports suggesting that subthalamic nucleotomy can be performed safely and successfully without inducing ballismus.[11] The procedure which has been reported with improvement in PD patients has the advantage of being easier to perform, cheaper than DBS and can be efficiently performed bilaterally.[12] It has been hypothesized that patients with PD are less prone to develop dyskinesia as a consequence of an STN lesion. Nevertheless, one out of 5 patients with a unilateral STN lesion developed a contralateral dyskinesia which had not disappeared 6-months after surgery.[13] Bilateral lesioning of STN, which is bordered by the corticobulbar and corticospinal tracts theoretically has a high potential to induce a pseudobulbar syndrome.[14] STN lesions have a neuroprotective effect on nigral cells in a rat model of parkinsonism. The possible mechanism of neuroprotection are related to excitotoxicity of the glutamatergic STN cells.[15]

Deep brain stimulation. The use of deep brain stimulation (DBS) for PD was first introduced in late eighties with the intention of providing an alternative to thalamotomy. In the last few years, the application of DBS has been extended to the GPi and STN.[16] The exact mechanism of action of DBS in PD is not precisely defined. It has been suggested that DBS

works by producing chronic neuronal depolarization; therefore, it may mimic the effects of lessoning but in a reversible mode.[17]

Ventral intermediate nucleus (VIN) deep brain stimulation. The indications for DBS of the VIM are similar to those for thalamotomy. It works in two-thirds of the patients. Successful thalamic stimulation allows patients to activities inhibited by tremor, such as handwriting and self-feeding. Successful procedures result in immediate relief of symptoms even during the testing of equipment in the operating room. Good tremor control with relatively low morbidity has been confirmed in several studies.[18-20] Surgical complications are similar to those mentioned for thalamotomy. Specific complications related to device are infections of the lead and the battery erosion of the subcutaneous tissue around the cable, and seroma at the battery site. A common adverse effect is paresthesia when the stimulator is turned on. In most patients this is transient

Globus pallidus deep brain stimulation. The role of DBS in the GPi is less well established, but the results appear similar to the pallidotomy results.[20] In a recent study of 38 patients with bilateral GPi-DBS evaluated in a double blind fashion, there was an average of 37% improvement in Unified Parkinsons Disease Rating Scale motor score, a 67% reduction in dyskinesia and relatively few complications.[21] Stimulation of the most ventral contact was found to inhibit not only levodopa induced dyskinesia, which could be completely suppressed using this contact, but also the action of levodopa, if stimulation parameters were experimentally increased.

Subthalamic nucleus deep brain stimulation. Deep brain stimulation of the STN seems to be procedure of choice in the treatment of severe motor complications in PD. Almost unique to the STN is the possibility of improving motor features that are not adequately controlled with medication, gait problems in particular, and the capacity to reduce levodopa dependence. Magnetic resonance imaging based stereotactic targeting based on direct visualization of the GPi or STN was found to be useful to improve target accuracy over that of indirect targeting methods. The intra-operative effect of microstimulation on rigidity can be reliably monitored and is predictive of the final clinical benefit on all Parkinsonian symptoms.[22] Dopaminergic drugs could be reduced by half with a consequent reduction in dyskinesia. Preliminary reports on the long term effects up to 4-years has also shown sustained effects.[23] This therapy may be considered as a breakthrough for PD patients with advanced stage disease, suffering from severe long term motor complications of dopaminergic treatment. Risks and side effects are similar to those mentioned for GPi. Overall DBS of the STN provides a striking improvement in quality of life, and some patients regain almost normal motor capacity.

Ablative surgery or deep brain stimulation. The decision-making. The observation that surgery of the STN and the GPi also has a profound anti tremor effect has led to a substantial reduction in thalamic VIM surgical procedures. Even patients whose primary complaint is tremor may be expected to progress and develop other symptoms of PD with time. Pallidotomy GPi is a proven and apparently durable treatment but involves creating a permanent lesion. If the lesion is incorrectly placed, it may result in little or no benefit and may cause adverse effects, such as visual field defects though such complications are rare in experienced centres. Pallidotomy does have the advantage of being a single procedure. A well-placed lesion results in significant benefit; patients have no implanted hardware and do not need stimulator adjustments. The GPi stimulation is relatively comparable with pallidotomy and may be used bilaterally. Choosing between STN and the GPi cannot be based on data as there is no large prospective, controlled study comparing both targets. Clinically, the only well established difference is that surgery of the STN may allow a drastic reduction in daily requirements of levodopa, whereas surgery of the GPi does not. Theoretically, the STN has a larger capacity than the GPi to influence neuronal activity at different levels of the basal ganglia, thalamus and brain stem. Whether this is clinically relevant has not be ascertained. The clinical efficiency of lesioning or implanting of electrodes in the VIM, GPi and STN seems almost identical. The major advantage of DBS is when considering bilateral surgery to avoid the potentially high rate of complications associated with bilateral lesions. Conversely, DBS imposes the extra cost of the device and is enormously labor consuming. It is also more hazardous than lesioning with regard to the occurrence of infections and problems with the lead and battery. In patients who live far away from a referral centre, the practicalities associated with DBS may be enormously cumbersome.

Neural transplantation. A number of studies have shown that bilateral and unilateral implantation of fetal mesencephalic tissue can induce substantial long-term functional improvements in patients with parkinsonism and severe dopamine depletion and is accompanied by increased uptake of fluorodopa by the striatum.[13-15,24]

In patients with PD unilateral grafts alone can give rise to bilateral effects.[25] The improvements have been most pronounced in the limbs contralateral to the graft, but ipsilateral amelioration of parkinsonian symptoms and reduction of the duration and number of "off" periods (when patients have bilateral symptoms) have been observed. The most likely explanation for the symptomatic relief on both sides is that a major output from the striatum is, through the pallidium and thalamus, directed to the

supplementary motor area, which has bilateral connections. Using positron emission tomography it has been shown, that well developed dopaminergic grafts in patients restored the impaired activation of the supplementary motor area.[26] Thus while the prospects are promising, further investigations aimed at improving and refining existing transplantation paradigms are warranted before neural transplantation techniques can be of widespread value.[27]

The available clinical data strongly supports the concept that restorative strategies will become of value for the treatment of large numbers of patients with PD. Besides ethical reasons the major obstacle to widespread application of neural transplantation is that, at present tissue from several human embryonic donors is necessary in each patient to induce a substantial clinical improvement. It is crucial that the use of human embryonic brain tissue for transplantation purposes be minimized by, for example, the development of xenograft approaches or genetic engineering or expansion of dopamine releasing neurons from stem cells or precursor cells.[28,29]

In conclusion, at present, it is difficult to unequivocally recommend one technique over the others. A number of factors must be considered including patient's age, primary source of disability and the patient's wishes. In general, pallidal stimulation might be preferable for patients who suffer from dyskinesia as a major source of disability and pallidotomy might be appropriate in cases where frequent stimulator adjustments are impractical. The STN stimulation may be more suitable for patients with significant disability "off" medications and in younger patients in whom it may be desirable to maintain intact circuitry so that newer treatments for example, neural transplantation, genetic engineering may be used as they become available.

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