9 Surgical Management of Parkinson's Disease

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Introduction

The mainstay of treatment of Parkinson's disease (PD) is based on dopamine replacement therapy which relieves most of the motor symptoms in the majority of patients for at least a few years. Nevertheless, some patients after a few years of dopamine replacement treatment develop disabling symptoms that are either not satisfactorily controlled, or arise as a direct result of dopamine replacement treatment. These individuals may benefit from surgery that aims to continuously deliver high frequency electrical stimulation of deep structures within the brain known as "deep brain stimulation" or DBS.

DBS was first developed as a way of treating patients with tremor that was refractory to drug treatments. A few pioneers of the technique showed beneficial effects through the accurate placement of electrodes in the motor thalamus.[1] The same procedure has been applied to two further areas within the brain known as i) the globus pallidus pars interna (GPi) and ii) the subthalamic nucleus (STN), for patients with PD suffering from fluctuations in the control of their motor symptoms with disabling off-phases, or with severe Levodopa induced dyskinesias. The STN is presently the most frequently used target.

Who can benefit from what types of DBS?

The success of this treatment is largely dependent upon the selection of patients that are most likely to benefit, and meticulous surgical technique. Patients should be chosen according to the nature of their most disabling symptoms, which should be likely to be improved by the procedure, and weighed against the known (individualised) risks.[2]

Thalamic DBS

The main **benefit** of DBS of the motor thalamus (ViM nucleus) is to improve tremor in the patient's contralateral hemibody. Beneficial effects on tremor suppression can persist beyond 6 years.[3] In parallel with improvement in tremor scores, activities of daily living and quality of life can also improve,[4] although these benefits seem to diminish in the long term. A randomised study of thalamic DBS against thalamotomy with blinded assessments of response has confirmed the superiority of thalamic DBS both in the short term[5] and long term.[6] While tremor suppression is effective after either procedure, neurological side effects such as cognitive deterioration or gait/balance disturbances are higher after thalamotomy. Furthermore, thalamic DBS can be performed bilaterally, whereas bilateral thalamotomy is no longer performed because of high complication rates including disturbance of speech and gait.

Axial features like gait and postural instability do not improve after thalamic DBS and the majority of patients require the same medication regime following surgery. Off medication dystonia and levodopa-induced dyskinesias are mostly unchanged. With the progression of neuronal loss in PD, patients remain at risk of developing the other symptoms of advanced PD such as motor fluctuations and dyskinesias. This should be considered in the initial decision regarding the choice of surgical target for each patient and thus the thalamic target is generally reserved for those patients not suitable for STN DBS operations.

The commonest **side effects** that occur as a result of unilateral stimulation of the ViM nucleus are speech deterioration (20%) and balance impairment (up to 10%).[7] These side effects happen far more commonly if the stimulation is delivered bilaterally[8] and among those patients who had impairments of speech or balance prior to surgery. A unilateral procedure or staged bilateral procedure can thus be a wise precaution in those patients that show evidence of speech or balance impairments, with the second side

only operated in individuals showing no deterioration following the first implantation. Transient sensory symptoms (paraesthesiae) are often reported by the patient when the stimulation is initially switched on, disappearing within the first few seconds or minutes. Very few neuropsychiatric or cognitive problems have been reported, although there have been only few studies in small groups of patients that have specifically looked for deficits in these aspects.

While ViM DBS can be associated with long-term improvement, tolerance associated with recurrence of tremor can occur with continuous stimulation. This can be overcome initially by increasing the stimulation voltage but ultimately patients' tremor can become resistant to even very high voltages, therefore many centres advise that patients should switch the DBS system off at night from the outset to prevent this occurring. This intermittent pattern of stimulation will also help prolong battery life. Since tremor tends to disappear during sleep irrespective of stimulation, this is often an acceptable way of preventing tolerance occurring. However, in certain patients an immediate worsening of tremor can occur as a rebound phenomenon when the stimulation is switched off and in a few patients this can prevent falling asleep and limit the possibility of an intermittent pattern of use. Rebound tremor occurring as a result of unexpected battery exhaustion will usually settle back to baseline levels of severity within a few days.

Pallidal DBS

All studies in the literature have demonstrated that GPi DBS has a major direct **benefit** on levodopa-induced dyskinesias.[9-12] This effect is maintained with prolonged follow up (continued 64% improvement at 5 years). Reports on the effect on the off symptoms of PD, suggests greater variability and a lower mean overall effect than STN DBS[13] that tends to disappear in the first few years of follow up irrespective of progressive increases in the stimulation parameters. Non-randomised comparisons of patients undergoing bilateral STN or GPi DBS showed mean improvements of off medication UPDRS motor scores of 32-39% at 6-12 months post operatively in the GPi group compared with 48-71% improvements in the STN groups.[14-16] In randomised comparisons of GPi and STN DBS, no overall advantage has been demonstrated by using DBS of one target rather than the other, although it is generally accepted that GPi has a greater effect on dyskinesia reduction while STN has a greater effect on off symptoms and signs.[16,17] Although some improvements in off symptoms following GPi DBS undoubtedly occur, it is interesting to note that patients receiving GPi DBS tend to have a negligible reduction in their dopaminergic medications in comparison with those patients receiving STN DBS. Some patients can even usefully increase the dose of dopaminergic medications following surgery if dyskinesias were a dose limiting factor beforehand.

There are far less data published regarding the effects of GPi DBS than STN DBS, since the STN target was rapidly adopted by many centres following initial suggestions of its more reliable effect on off symptoms. Quality of life measured before and following GPi DBS has been shown to improve markedly at 6 months although this improvement lessens if patients are re-evaluated at 3 or 4 years.[18] The apparent advantage of STN DBS (particularly in improving bradykinesia) should be considered even among patients with minimal disability from off symptoms at the time of surgery, as these symptoms may subsequently evolve with time. Patients with severe dyskinesias who are considered not suitable for STN DBS are preferred candidates for GPi DBS, however, it remains possible to perform successful STN DBS and relieve off symptoms even among patients that have had previous GPi DBS.[19]

The commonly reported **side effects** following GPi DBS relate to the local anatomy. Spread of current beyond the medial border of the GPi to the internal capsule can cause dysarthria, or involuntary muscle contractions, usually affecting the contralateral face or upper limb. Stimulation spreading beyond the ventral border to the optic tract can lead to a perception of flashes in the contralateral visual field. Stimulation parameters which are too high especially in the ventral GPi can lead to an exacerbation of parkinsonism.[9] Other side effects include transient paraesthesiae, dysphagia, weight gain, and eyelid apraxia. Cognitive decline and psychiatric problems are less common and make this target more

appealing among patients in whom there are concerns re previous cognitive or psychiatric symptoms. In the few published studies comparing patients implanted in the GPi with patients implanted in the STN, there are generally fewer side effects with GPi DBS than STN DBS.[16,17]

Subthalamic DBS

The STN was rapidly adopted as the preferred DBS target for PD because of the immediate and marked **benefit** on most of the off motor symptoms. Resting and postural tremor of the limbs, jaw and head, limb and truncal rigidity, and limb or axial bradykinesia/akinesia can all improve. Gait dysfunction including loss of arm-swing, off period freezing, and postural instability improve most reliably if pre-operatively these symptoms and signs were restricted to off periods and improved during on periods.[11,20,21] The severity, frequency and pain arising from drug-induced dyskinesias can all improve in the long term, largely related to the reduction in drug dosage. Drug dosage is on average reduced by 50% 12 months after surgery. Improvement in motor performance is usually accompanied by improvement in functions including manual dexterity, handwriting, and other activities of daily living. Achieving optimal clinical improvement following STN DBS requires experience of the adjustment of stimulation parameters and drug dosage and timing. It is often necessary to reduce the total daily dose of dopaminergic medications to allow progressive increases in electrical parameters, since combinations of previously required drug doses when administered together with electrical stimulation can cause an acute exacerbation of dyskinesias. Off period dystonia experienced in the early morning, or as drug levels subside can also improve, dramatically in some patients.

Published long-term data are available for cohorts of patients with greater than 5 years of follow-up.[22,23] Beneficial effects persist on both off motor symptoms and dyskinesias, despite continued progression of the underlying neurodegenerative process. At 5 years, patients are on average still 50% better than they were before surgery and markedly better than with the stimulation switched off. As with non-operated patients with advanced disease, with the passage of time there is worsening of motor symptoms in particular the axial features both on and off drug.

There is an increasing literature on the effect of STN DBS on non-motor symptoms. Sleep generally improves, largely because patients are more comfortable and can turn more easily in bed.[24] A few small studies have reported improvements in discriminating smells following STN DBS.[25,26] In contrast to levodopa, STN DBS has little or no effect on postural hypotension.[27] There have been a few studies in small numbers of patients, on the effect of STN DBS on bladder function with the majority indicating beneficial effects.[28] There are less data on the effects on sexual function. Increased libido can be seen, in particular, in the early stage. Patients with dopamine dysregulation and impulse control behaviour have a chance to improve after surgery, largely by allowing drug dosage reduction. However increased impulsivity has also been seen in the early post-operative days and such patients should be closely monitored by carers and friends to ensure impulsive decisions do not have negative consequences.

Alongside changes in motor function, the mean change in quality of life has been evaluated following STN DBS in several studies, including a randomised controlled trial against best medical treatment.[29] Using the standard PD quality of life scale (PDQ-39), there was an improvement of 9.5 points in favour of the STN surgery. There is some evidence that quality of life improvements correlate more closely with improvement in depression rather than motor function.[30,31] The mean outcomes of surgery are not necessarily applicable to all patient groups. In a small open study,[32] it was shown that improvements in motor complications seen in older patients (>65 years) are not always accompanied by improvements in quality of life, probably due to negative effects on axial motor symptoms.

The most common **side effect** specifically related to the STN target is deterioration of speech intelligibility that is in part related to electrical parameters and precise location of the electrode within the STN target.[33] Weight gain can occur following surgery through an unknown mechanism but can be avoided or reversed with appropriate dietary advice. Neuropsychiatric problems are not unusual, with depression, mania, and apathy all reported and these are more likely to occur among patients with a

history of psychiatric disease. Cognitive decline has been described, and in a comparison between STN operated patients and PD controls seems to be particularly related to decreases in verbal fluency.[34]

Surgical Complications

The most serious surgical complication is intra-cerebral haemorrhage. Not all haemorrhages seen on post operative scans are associated with symptoms, but this remains the greatest potential risk as this can be associated with stroke, paralysis or death. The frequency of haemorrhage is variable between series with a meta-analysis reporting symptomatic haemorrhages occurring following 2% of procedures and asymptomatic haemorrhage following another 1.2%.[2] Both the pulse generator and electrodes are at risk of infection, and in the case of the latter can rarely lead to the development of brain abscess. Seizures are rare but can occur in patients with or without a history of epilepsy. Post operative confusion is not uncommon and likely has multiple contributory factors including oedema related to the electrode, prolonged periods without medication during surgery, or hangover effects from general anaesthesia.

Patient Selection and Choice of Target

Careful patient selection aims to ensure that the patients undergoing surgery are indeed likely to benefit, by clarifying which of their symptoms are most troublesome and advising whether these are likely to be helped by the surgery, alongside assessing whether their individual risks are outweighed by the potential benefits. STN DBS is currently the most common target for stimulation, but there is still a place for both thalamic and GPi DBS in selected patients. As part of this process, each patient should undergo a levodopa challenge to assess the reversibility of symptoms and signs. Parkinsonian features that improve with levodopa are likely to also improve with STN DBS, whereas signs that do not improve are unlikely to respond to STN DBS. The exception is tremor which can improve following DBS even if refractory to levodopa. All patients should also have a comprehensive cognitive assessment and an MRI of the brain. Any patient with signs or symptoms suggesting significant pathology outside the brain that may require MRI imaging (e.g. suspicion of cervical myelopathy) should have appropriate scans performed prior to DBS.

Patient Information

Patient information is very important at every stage of this procedure. Patients often have very high expectations from DBS and as a result some patients with acceptable clinical outcomes may be disappointed if their pre-operative expectations were unrealistic. Taking the time to explain in a very clear way, exactly what the potential benefits and risks from surgery might be is a vital part of the process.

Following surgery there are only few restrictions on most daily activities. MRI scans of certain body regions can be performed only under specific conditions and in some cases may be impossible. The use of monopolar diathermy (electrocautery) is contra-indicated, and the contact details of the DBS team should be made readily available to clinicians subsequently involved in the patients care, to provide advice on alternative surgical techniques. Patients subsequently undergoing invasive procedures that may lead to transient bacteraemia (including dentistry) are at risk of infection colonising the implanted hardware, therefore prophylactic antibiotics are advised. Routine investigations such as X rays, mammography or diagnostic ultrasound scans are possible, but in the case of any doubt, the hardware manufacturer or implanting DBS centre should be contacted.

Main Trouble Shooting

There are many potential problems that might be encountered during the follow-up of patients with DBS.

Skin

It is important to monitor wound healing over the battery, the cable connectors and the electrode caps on the skull, specifically looking for early signs of hardware eroding through the skin or developing infection. The patient should be encouraged to contact the implanting centre or their local neurologist if they have any concerns. Infection, if it occurs is most likely within the first few months following surgery (including battery changes) but can also occur very late, in particular, following transient bacteraemia. Surgical hardware eroding through the skin is unusual but is most commonly seen on the skull. Some patients can experience discomfort from the sensation of "pulling" of the battery or cables. If persistent this can be revised surgically, but as this inevitably carries an additional risk of infection, and thus if it is tolerable, should only be done when the battery requires changing.

Sudden Failure

Acute worsening of PD symptoms in a DBS patient should be treated as an emergency, in particular, among patients treated with STN DBS. Patients can develop a state of severe parkinsonism that may be unresponsive to both levodopa and apomorphine and requires restarting of the DBS. In these circumstances, the first step is to check if the battery is on and still delivering current. If the battery has reached its end of life, it is completely unresponsive to interrogation and it should be changed immediately. If the battery is still functional and cannot reveal the source of the problem, the integrity of the system should be checked by impedance checks and plain X-rays of the connectors and electrodes.

Progressive Reduction of Benefit

Among patients reporting a gradual and partial reduction in benefit, the first question is whether the symptoms can be helped further by adjusting medications and/or stimulation. The patient can be assessed off medication to independently evaluate the effects of stimulation and attempt to optimise symptom control with a systematic adjustment of stimulation parameters. The subsequent response to a levodopa challenge and if necessary planning of further stimulator adjustment sessions can help ensure maximum symptom control is achieved. Over the passage of time, some symptoms, in particular, axial symptoms such as postural instability and freezing become less sensitive to dopaminergic medications as well as DBS. A subset of patients develop axial features such as gait freezing seemingly made worse by long term high frequency STN DBS. These features may improve by lowering the DBS frequency.[35]

Dyskinesias

In the early post operative stages following STN DBS, dyskinesias can be difficult to improve and may worsen, requiring close supervision to balance the patient's medications and stimulation. In the medium to long term dyskinesias tend to improve, and in most patients it becomes possible to slowly increase the stimulation voltage in parallel with reduction in medication.

Dysarthria

Dysarthria is a common side effect of bilateral DBS surgery. It is a complex problem with multiple factors contributing to its development. The electrical parameters can play a role with higher voltages (above 4 V), and higher pulse widths (above 90μs), both contributing. In some patients, dysarthria necessitates the choosing an alternative contact which may have less beneficial effects on other motor symptoms. In parallel with DBS adjustment, patients with any speech impairment should be seen by an experienced speech therapist and given exercises including formal Lee Silverman Voice training (LSVT).

Neuropsychiatry

Neuropsychiatric problems are common in the advanced stages of PD, particularly among the DBS population who frequently have had early onset and severe PD. Many factors contribute to the development of depression, hallucinations, psychosis or paranoia including a role of medications, the stimulation itself, undergoing invasive brain surgery and the need to attend hospital regularly, an

individual's support network and family environment, together of course with the individual's background personality and psychiatric history.

The presence of depression and impulsivity following DBS combine to a risk of suicide that has to be taken very seriously. A review of suicide risk following STN DBS found completed suicide rates of 0.45%, and attempted suicide rate of 0.9%.[36] The risk of suicide seems to be lower following GPi DBS but nevertheless has been reported in a patient undergoing GPi DBS for dystonia.[37] Depressive symptoms rarely improve by adjustment of DBS parameters but it is clear that excessive reduction in dopaminergic medications can lead to depression, and apathy.[38] If reinstatement of dopaminergic therapy is insufficient, then antidepressant medications are required.

Both mania and impulsivity may occur more directly as a result of stimulation and can be ameliorated by adjustment of electrical DBS parameters, by reducing voltage or changing the electrical contact. These symptoms can also occur as an interaction between stimulation and previously tolerated dopaminergic medications (particularly the dopamine agonist drugs), and thus may also improve with medication reduction.

New Developments in DBS Technology

The manufacturers of DBS hardware have introduced new designs of electrodes and pulse generators in an attempt to help improve the outcomes of DBS surgery. These include:

1. Directional DBS electrodes using segmented electrical contacts. This innovation allows the programmer to steer the electrical current laterally/medially, anteriorly or posteriorly according to optimal benefits/side effects.
2. Rechargeable Pulse generators allow the implanted devices to be smaller, therefore less conspicuous and with a lifespan of up to 25 years. The patient (or their carer) must have the physical and cognitive ability to recharge the pulse generator (battery) using their own recharger for about an hour per week.
3. MRI conditionality. The newest DBS systems allow limited MRI sequences to be performed provided strict safety conditions are followed.
4. Multiple independent current sources allow different parameters to be programmed on different contacts according to optimal benefits and side effects.

While there is little evidence that these advances have yet translated to improved outcomes, especially among patients who have perfectly placed DBS electrodes, intuitively these innovations should all contribute to improved options for optimal symptom control.

Conclusions

DBS is a proven technique to improve motor symptoms in patients with advanced PD. Whether there is a role for surgery in the earlier stages of PD remains to be established. While there is no evidence that the surgery halts the neurodegenerative process, there is no doubt that the complications of dopaminergic therapy in advanced PD patients can be significantly helped and thus can maintain independence and quality of life in well-selected patients.

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