Stereotactic Microelectrode-guided Posteroventral Pallidotomy and Pallidal Deep Brain Stimulation for Parkinson's Disease

A K Y Tan,*FAMS, MBBS, MRCP (UK), T T Yeo,**MBBS, FRACS (Neurosurg), H T L Tjia,***FAMS, MBBS, M Med (Int Med), S Khanna,****PhD, W L Nowinski,†PhD

Abstract

Three patients underwent stereotactic posteroventral pallidotomy, and 1 patient underwent pallidal deep brain stimulation, for medically intractable symptoms of advanced Parkinson's disease, characterized by peak-dose levodopa dyskinesias, wearing-off fluctuations, tremor, rigidity and bradykinesia. Surgery was performed stereotactically under local anaesthesia, with eventual target coordinates derived from a combination of magnetic resonance imaging (MRI), coregistration with an electronic brain atlas, intraoperative microelectrode neuronal recordings and microstimulation before lesioning or placement of a deep brain stimulator was done. Assessment was made at baseline preoperatively and at 3-month intervals postoperatively, with Unified Parkinson's Disease Rating Scale (UPDRS) and Core Assessment Program for Intracerebral Transplantation (CAPIT) scoring. All patients improved in dyskinesia, tremor, rigidity and bradykinesia contralateral to the lesion side, but also on the ipsilateral side to a lesser extent. The improvement was largely seen in the 'off' state: UPDRS by 41%, and CAPIT by 19% on the contralateral side. 'On' freezing was not helped. There were no deaths and no visual complications, but there was one complication of a delayed contralateral upper limb dystonia after pallidotomy. The 1 patient with pallidal deep brain stimulation (DBS) obtained similar improvement as those with pallidotomy. Posteroventral pallidotomy and pallidal stimulation improves all the cardinal features of Parkinson's disease, and effectively ameliorates levodopa dyskinesias.

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Introduction

Medications for Parkinson's disease (PD) is effective for several years, but is followed by motor fluctuations, dyskinesias and progression of bradykinesia and rigidity. This is the reason why surgical therapies for PD have enjoyed a resurgence of interest. Historically, surgical treatment for PD began in the 1930s, in the pre-levodopa period, when Putnam[1,2] sectioned the pyramidal tracts of the spinal cord and Bucy[2,3] removed portions of the motor cortex. This improved tremor and rigidity, but produced limb weakness.

Meyers,[4] in the late 1930s, pioneered extrapyramidal tract surgery and began by experimenting with resection of portions of the basal ganglia. He showed that tremor and rigidity could be improved, without producing limb weakness by not affecting the corticospinal/pyramidal tract. Cooper,[5] while attempting to perform an open pedunculotomy in a patient with PD, had to ligate the anterior choroidal artery, causing a globus pallidus infarct, and he serendipitously noted improvement of contralateral parkinsonian signs. In 1947, Spiegel and Wycis first introduced stereotactic surgical techniques in humans.

In 1952, Narabayashi and Okuma,[6] using their own stereotactic apparatus, gave procaine oil injections into the GP for patients with PD. In 1953, Guiot and Brion[7] reported on electro-coagulation of the pallidum. Svennilson et al[8] began performing anterodorsal

* *Consultant*
Department of Neurology
** *Consultant*
*** *Senior Consultant and Head*
Department of Neurosurgery
Tan Tock Seng Hospital
**** *Senior Lecturer*
Department of Physiology
National University of Singapore
† *Laboratory Director*
Biomedical Laboratory
Kent Ridge Digital Laboratories
Address for Reprints: Dr Adrian Tan, Department of Neurology, Tan Tock Seng Hospital, Moulmein Road, Singapore 308433.
E-mail: adrian_tan@notes.ttsh.gov.sg

pallidotomies in 1952, but were disappointed with the results and found that they could obtain better results by shifting the target to the posteroventral part of the pallidum. The pallidal target was however abandoned by most other neurosurgeons when Hassler and Riechert[9] demonstrated dramatic improvement in tremor when a lesion was placed in the ventrolateral thalamus. From 1966 onwards, after levodopa was introduced, there was a long and sharp decline in surgery for PD and this led to its eventual demise for the next two decades, until its recent resurgence of interest in the 1990s.

This resurgence of interest was largely due to Laitenen et al,[10] who published their results of posteroventral pallidotomy in 38 PD patients in a landmark article in 1992. They reported complete or almost complete relief of rigidity and bradykinesia in 92% of their patients. Dopa-induced dyskinesias were also markedly improved.[10] Several papers followed[11-13] demonstrating the efficacy of this technique, and some of these groups have shown that by utilizing microelectrode recordings, complications can be minimized and target localisation optimized. Against this background, we report our initial preliminary findings, at 3 months after surgery, on a small series of 4 local patients who underwent either a posteroventral pallidotomy or pallidal deep brain stimulation (DBS) using stereotactic microelectrode guidance.

Materials and Methods

Protocol approval was obtained from the Ethics Committee of Tan Tock Seng Hospital. Written informed consent was obtained from the patients for the surgical procedure and neuronal microelectrode recordings. PD was diagnosed when there were at least 2 out of 4 cardinal signs, namely rest tremor, rigidity, bradykinesia and gait disturbance / postural instability.

The inclusion criteria were patients with idiopathic PD, and who were at least Hoehn and Yahr stage III when 'off'. The patients must have had at least 30% response after oral levodopa. 'On' state refers to antiparkinsonian medications producing symptom alleviation and improvement in the patient. 'Off' state occurs when the effects of medications have worn off. The following exclusion criteria were employed:

1) dementia,
2) signs of atypical parkinsonism such as supranuclear gaze palsy, ataxia and significant orthostatic hypotension, and
3) past history of encephalitis, severe head trauma or prolonged neuroleptic use.

Four patients were studied, with 3 undergoing posteroventral pallidotomy and 1 deep brain pallidal stimulation with a Medtronic Itrell II implantable pulse generator (Medtronic, Minneapolis, MN, USA). There were 3 females and 1 male, and the mean age was 50.3 years (range 45 to 53 years). The mean disease duration was 7.2 years (range 6 to 10 years). The major problems which these patients experienced were levodopa-induced dyskinesias and severe wearing-off.

Patient Assessment

The patients were assessed according to the Core Assessment Program for Intracerebral Transplantation (CAPIT)[14] timed tests: pronation-supination, hand-arm movement between two points, finger dexterity and walk. UPDRS scores were determined. They were also assessed at baseline and every 3 months for a total of 1 year. CAPIT scoring is used in trials of fetal transplantation and many trials of stereotactic pallidotomy or deep brain stimulation. It is a series of timed tests which include speeds of doing a set of finger tapping, arm pronation and supination, tapping 2 points 30 cm apart, and walking 7 m and back. These tests are reproducible and do not require expensive equipment. The UPDRS is a validated scale of comprehensive assessment of a PD patient in the areas of mentation, rigidity, bradykinesia, postural stability, activities of daily living and complications of therapy. There are 35 questions with a 0 to 4 scale with '0' indicating no symptoms or signs, to '4' being very severe. There are 7 questions with 'yes' or 'no' options.

Recordings were made at 12 hours without medications, and during their best 'on' state. The medication dosages were kept unchanged for 4 weeks before surgery, and maintained at similar dosages, as far as possible, after surgery.

Surgical Procedure

This has been described in some detail in another publication[15] and will only be discussed briefly here. All antiparkinsonian medications were withdrawn 12 hours before the surgery. Under local anaesthesia, a Radionics MRI-compatible CRW stereotactic frame with localizing fiducials was attached to the patient's head with the base ring placed as far as possible parallel to the anterior commissure-posterior commissure (AC-PC) plane. A 1.5 Tesla MRI scanner (GE Signa Horizon) was used to obtain sagittal T1-weighted spin-echo localizer scans to identify the anterior and posterior commissures. Axial three-dimensional Fast Gradient Recalled Echo (3D FGRE) study was then performed at 1 mm slice thickness from the level of the middle cerebral peduncle to above the level of the corpus callosum parallel to the AC-PC plane. The images were then transferred to a Silicon Graphics Reality Engine Workstation where a resident Schaltenbrand and Wahren brain atlas developed locally[16,17] was installed and this was used to help in target localisation.

The tentative anatomical target was generally close to that recommended by Laitenen: 3 mm anterior to the

mid-commissural point, 3 to 6 mm below the intercommissural line and 21 to 22 mm lateral to the midline. A pre-coronal frontal burr hole was made under local anaesthesia. The initial target was approached at 20° to 40° anterior to the patient's vertical axis. A high impedance 1.5 MΩ glass-coated platinum-iridium microelectrode with a tip diameter of one micron was used and neuronal recordings started about 20 mm superior to the target and extended to about 10 to 15 mm below the target. When units were identified, passive and active limb movements were performed to observe their effect on the modulation of neuronal activity. A strong flash light was used to test visual responses when the electrode was in the vicinity of the optic tract. A postero-ventral globus pallidus interna (Gpi) lesion was only made when the ventral and posterior borders of the Gpi were clearly identified, and where microstimulation did not evoke visual, motor or somatosensory responses. Three to 5 microelectrode tracks were usually required to define these borders neurophysiologically. The final target chosen was based essentially on the microelectrode findings, which is the present gold standard for neurophysiological localization. Lesion making was done for 60 s at 90°C using the Radionics radiofrequency generator for those patients undergoing a pallidotomy. During lesion making, the patient's speech, vision and motor function were tested. For the patient with pallidal stimulation, no lesioning was done, and instead, a quadripolar electrode (model 3387; Medtronic, Minneapolis, MN, USA) was implanted into the posteroventral Gpi, and then connected to a stimulator (Itrell II; Medtronic) placed in the subclavicular area.

Results

All patients demonstrated improvement of rigidity, bradykinesia and tremor after lesioning, and the patient with pallidal DBS obtained improvement after his pulse generator was switched on and adjusted to its optimal parameters. One patient developed an upper limb dystonia on the contralateral side 3 weeks after the surgery which was permanent. Postoperative MRI showed good lesion placement in the Gpi and did not show encroachment on to the globus pallidus externa (GPe). This dystonia was unresponsive to manipulation of oral medications. Her upper limb dystonia however improved with botulinum toxin injections. No patient developed visual field defects or pyramidal weakness.

There was a significant improvement in the tremor and rigidity subscores of the UPDRS. The CAPIT subtest scores were improved 19% on the side contralateral to the pallidotomy in the 'off' state (Table I). The ipsilateral side only showed a 7.3% improvement. The CAPIT scores in the 'on' state showed no significant difference before and after surgery. UPDRS motor scores in the 'off' state improved by 41% (Fig. 1). Again there was no difference in the UPDRS motor scores in the 'on' state.

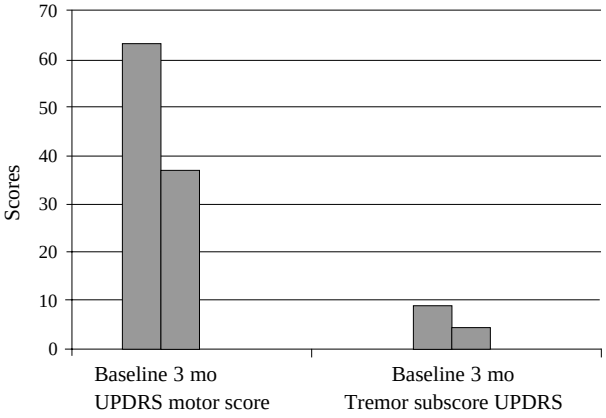

Fig. 1. UPDRS motor score in the 'off' state is reduced after pallidotomy by 41%. The tremor subscore of the UPDRS is also improved after surgery by 41%.

Levodopa-induced dyskinesias were almost completely abolished on the contralateral side, with a marked improvement on the ipsilateral side and axial region. The stand-walk-sit subtest of the CAPIT showed a significant improvement after pallidotomy. Two patients who were unable to walk unassisted in the 'off' state before the surgery were able to do so after pallidotomy (Table II). Medication dosages remained the same as was set out in the protocol, and it could not be determined if patients required less medications after surgery. The patient with pallidal DBS had the Itrel II pulse

TABLE I: MEAN CAPIT SCORES IMPROVED 19% IN THE CONTRALATERAL LIMBS POSTOPERATIVELY, AND 7.3% IPSILATERALLY

Patient	Contralateral		Ipsilateral	
	Baseline	3 mo PS	Baseline	3 mo PS
1	80.7	68.3	65	74
2	39.2	29.4	37.6	42.1
3	69.5	58.2	75.0	51.8
4	49.5	36.9	46.3	39.7
Mean CAPIT	59.7	48.2	56.0	51.9

CAPIT: Core Assessment Program for Intracerebral Transplantation; PS: post-surgery

TABLE II: STAND-WALK-SIT TIMINGS OF THE CAPIT TEST

	Before surgery		After surgery	
	Off	On	Off	On
1	Unable	15.1 s	Unable	14.7 s
2	246 s	14.4 s	132 s	13.0 s
3	Unable	21 s	27.6 s	17.9 s
4	Unable	Unable	29.3 s	21.7 s

CAPIT: Core Assessment Program for Intracerebral Transplantation

generator set at 1.0 V, frequency 160 Hz and a pulse width of 90 μs, and it was left permanently switched on.

Discussion

Our results corroborate with recent studies[11-13] that posteroventral pallidotomy and pallidal DBS improve contralateral dyskinesias, tremor, rigidity and bradykinesia, and to a lesser extent, symptoms on the ipsilateral side. Gait improved remarkably for 2 patients in the 'off' state. 'On' freezing was not helped by pallidotomy. Most of the benefit was seen in the 'off' period symptoms, but there was no substantial benefit during the 'on' state, except for peak-dose levodopa induced dyskinesias.

Using microelectrode recordings to locate the optic and pyramidal tracts resulted in no instances of hemiparesis or visual field defects. One patient developed a permanent contralateral upper limb dystonia at rest 3 weeks after surgery. There have been reports of lesions in the globus pallidus[18-20] causing dystonia and this is postulated to be due to loss of inhibitory pallidal projections to the thalamus which results in a hyperkinetic disorder. Our patient's postoperative magnetic resonance imaging of the brain showed that the lesion was in the standard location at the posteroventral portion of the internal segment of the globus pallidus and not in GPe. To our knowledge, this is the first report of dystonia as a complication of a properly-placed posteroventral pallidotomy for Parkinson's disease.

Two studies[11,12] have demonstrated that the benefits of pallidotomy are sustained at 1 year after surgery, and younger patients seemed to derive greater improvement than the elderly. In the study by Dogali et al,[11] UPDRS scores improved by 65%, and CAPIT scores on the contralateral limb by 38.2% and ipsilateral limb by 24.2% during the 'off' state. Patients with moderate to severe dementia benefited less from surgery.[13] Baron et al applied extensive neuropsychological tests to their patients undergoing pallidotomy and these did not show any significant change 6 months following surgery, except for the Backward Digit Span score which showed an improvement in attention. Swallowing improved throughout the follow-up period at 1 year, but postural stability and freezing worsened after an initial improvement at 3 months. A recent study found that unilateral pallidotomy resulted in a persistent contralateral improvement and unexpected ipsilateral improvement after 4 years.[21] PD symptoms did not appear to progress, even ipsilaterally, and the effectiveness of levodopa was maintained at almost the same dosage.

From studies of primates treated with 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP) to induce parkinsonism,[22] it was observed that dopamine depletion resulted in excessive neuronal activity in the subthalmic nucleus (STN) and GPi. Improvement of bradykinesia in these parkinsonian primates occurred after lesioning the STN. In humans, the GPi, is more accessible, with low mortality and morbidity, and does not cause hemiballismus as a lesion in the STN would. The reason for beneficial ipsilateral effects after unilateral pallidotomy is not clear. Some explanations include bilaterality of cortical projections onto the striato-pallidal-thalamocortical loop and bilateral pallido-thalamic projections.[23]

We conclude that GPi pallidotomy and pallidal DBS improves most of the cardinal features of parkinsonism, especially in the 'off' state, and a striking elimination of contralateral peak-dose levodopa dyskinesias in the 'on' state. Improvements are immediate. With microelectrode recordings, very precise lesioning can be achieved, with the avoidance of major complications. GPi pallidotomy and pallidal stimulation can be recommended for patients with advanced PD, who are still levodopa responsive, but suffer from severe motor fluctuations and dyskinesias.

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