Pallidal stimulation: an alternative to pallidotomy?

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A resurgence of interest in the surgical treatment of Parkinson's disease (PD) came with the rediscovery of posteroventral pallidotomy by Laitinen in 1985. Laitinen's procedure improved most symptoms in drug-resistant PD, which engendered wide interest in the neurosurgical community. Another lesioning procedure, ventrolateral thalamotomy, has become a powerful alternative to stimulate the nucleus ventralis intermedius, producing high long-term success rates and low morbidity rates. Pallidal stimulation has not met with the same success. According to the literature pallidotomy improves the "on" symptoms of PD, such as dyskinesias, as well as the "off" symptoms, such as rigidity, bradykinesia, and on-off fluctuations. Pallidal stimulation improves bradykinesia and rigidity to a minor extent; however, its strength seems to be in improving levodopa-induced dyskinesias. Stimulation often produces an improvement in the hyper- or dyskinetic upper limbs, but increases the "freezing" phenomenon in the lower limbs at the same time. Considering the small increase in the patient's independence, the high costs of bilateral implants, and the difficulty most patients experience in handling the devices, the question arises as to whether bilateral pallidal stimulation is a real alternative to pallidotomy.

Key Words • globus pallidus • pallidal stimulation • pallidotomy • Parkinson's disease

Pharmacological therapies are the current mainstay in the treatment of Parkinson's disease (PD). However, as the disease progresses the positive effects of the medication decrease and debilitating side effects may occur. The limitations of long-term pharmacological treatment have led to a renewed interest in surgical methods to relieve the major symptoms of PD: tremor, rigidity, and bradykinesia, as well as medication-induced side effects such as on-off fluctuations and levodopa-induced dyskinesias.

In the 1940s and 1950s, pallidotomy was an established procedure for the treatment of PD. Later pallidotomy was replaced by thalamotomy, which was favored by Hassler, Riechert, and Mundinger, because thalamotomy seemed to be superior to pallidotomy for suppression of tremor. After the introduction of orally administered levodopa, functional neurosurgical procedures began to decline. Patients' low tolerance to long-term drug treatment and the occurrence of motor and psychiatric side effects, coupled with improved imaging modalities and a better understanding of the neuroanatomy and neurophysiology of the basal ganglia, have led to a resurgence of interest in surgical procedures to relieve parkinsonian symptoms. The resurrection of pallidotomy followed two papers by Laitinen and colleagues, who described the long-term outcome of Leksell's series in the 1950s and 1960s. Since that time, many more than 1000 patients have undergone ventrolateral pallidotomy with promising short- and long-term results.

Although ventrolateral thalamotomy for the treatment of drug-resistant parkinsonian tremor has been replaced in many neurosurgical centers by stimulation of the nucleus ventralis intermedius (VIM), as introduced by Benabid, Siegfried, and others, bilateral pallidotomy is still considered an experimental procedure by many neurologists and neurosurgeons. Given the low morbidity rates engendered by stimulation procedures compared with lesioning methods, especially bilateral procedures, the benefits of this new method should be evaluated. There was an initially encouraging paper published in 1994 reporting a small number of patients, but other investigators have not been able to replicate the results.

In this study we report a small series of six patients who underwent bilateral pallidal stimulation. Although considerable improvement in their "on" symptoms (that is, dyskinesias) was observed, only slight improvements in their "off" symptoms (that is, gait disturbance and bradykinesia) were noted. Depending on the stimulation intensity, gait was worsened by creating a freezing phenomenon, which limits the use of the stimulation devices.

Clinical Material and Methods

Patient Selection

In a series of 25 patients treated with chronic electrical stimulation for movement disorders, six patients (Table 1) underwent operation with bilateral pallidal stimulation in the posteroventral pallidum. The patients' mean age was 61.7 years (range 47–69 years). The duration of disease varied from 3.5 to 19 years (mean 13.8 years).

Preoperative Evaluation

All patients with drug-resistant or drug-induced symptoms had a presurgical hospital stay of 3 to 4 weeks in the
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Surgical Procedure

Pallidal stimulation was performed using the Zamorano–Dujovny stereotactic system (Howmedica-Leibinger, Freiburg, Germany), guided by magnetic resonance (MR) imaging. The last dosage of medication was given to the patient the evening before surgery. The procedure was performed while the patient was in the “off” state. The surgical procedure was performed after the patient received a local anesthetic and with continuous intravenous sedation and analgesia during application of the frame. The patient was conscious throughout the procedure. The patient did not receive medication during the imaging, microrecording, or stimulation phases of the operation.

An MR-compatible frame was applied to the patient’s head, according to external landmarks, to be as parallel as possible to the intercommissural (IC) line. Magnetic resonance images were obtained using a 1.5-tesla imager. A midsagittal image was obtained and the deviation of the head frame to the IC line was determined; axial slices were then obtained parallel to the IC plane. The pallidal target was chosen 2 to 3 mm anterior to the midcommissural point, 19 to 22 mm lateral to the midline, and 3 to 6 mm below the IC line. The target was corrected using the angle deviation between the frame and IC line. Two pre-coronal burr holes were drilled 2.5 cm lateral to the midline. This created a trajectory between 3˚ and 10˚ with reference to the sagittal plane and 40 to 52˚ with reference to the anterior commissure to posterior commissure line. Beginning 10 mm above the pallidal target, recordings were obtained with concentric bipolar tungsten microelec-

neurology unit to optimize their medical treatment. During this time extensive tests, including neuropsychological evaluation and rating, neurophysiological tests (somatosensory evoked potentials and visual evoked potentials, transcortical magnetic stimulation, tremor analysis, and long-loop reflexes) were performed. Clinical ratings according to the Core Assessment Program for Intracerebral Transplantation (CAPIT) recommendations, including timed movement tests, the complete Unified Parkinson’s Disease Rating Scale (UPDRS), and dyskinesia score were obtained at regular intervals, when the patient was in worst “off” and best “on” conditions. Patients were videotaped during the different states. Finally a perimetric examination was performed by an ophthalmologist to document any postoperative changes in the visual field.

### Summary of characteristics in six patients with PD

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Duration of Disease (yrs)</th>
<th>Hoehn &amp; Yahr Score</th>
<th>Medication Dosage (mg)</th>
<th>Follow-Up Period (mos)</th>
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<tbody>
<tr>
<td></td>
<td>Sex</td>
<td></td>
<td>Preop (off)</td>
<td>Postop (off)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>65, M</td>
<td>3.5</td>
<td>II (III)</td>
<td>III (III)</td>
<td>levodopa 550</td>
</tr>
<tr>
<td>2</td>
<td>60, M</td>
<td>19</td>
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<td>III (III)</td>
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<tr>
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<td>47, M</td>
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<td>II (III)</td>
<td>levodopa 700; lisuride 1</td>
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<tr>
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<td>III (IV)</td>
<td>levodopa 1150; selegilin 10; lisuride 1.4; amantadin 700</td>
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<tr>
<td>6</td>
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<td>18</td>
<td>III (IV)</td>
<td>III (IV)</td>
<td>levodopa 720; pergolide 4; biperiden 2; selegilin 10</td>
</tr>
</tbody>
</table>

TABLE 1

Results

The results of bilateral pallidal stimulation are present-
ed in Figs. 1 to 4. Scores on the Hoehn and Yahr scale in six patients did not show any obvious improvements after surgery either in the off or on state (Fig. 1). No differences were demonstrated when comparing the CAPIT time testing (pronation–supination, finger tapping, and finger dexterity) of the upper extremities in the presurgical off state with the postsurgical results either with stimulation on or off. An improvement was seen in the lower extremities postsurgically in the off state but it was independent of whether the stimulator was on or off. This might represent a micropallidotomy effect or a prolonged stimulation effect after the stimulator was switched off (Fig. 2 left).

When the stimulator was turned on, there was a slight worsening in the lower-extremity function in the on state. This was primarily because of the freezing episodes, which depended on the stimulus intensity (Fig. 2 right). The motor examination scale (MES) score of the UPDRS was unchanged in the off state (Fig. 3 left) and worsened in the on state, more markedly with the stimulator on due to increasing freezing episodes (Fig. 3 right).

The only significant improvement was seen in the dyskinesia score. Although postsurgically a small improvement was seen when the stimulator was turned off (possible micropallidotomy effect), a significant improvement was demonstrated with the stimulator turned on (Fig. 4).

Discussion

Clinical Improvement

Considering our results with bilateral pallidal stimulation and the results of posteroventral pallidotomy reported in the literature, discrepancies are obvious. The main difference is that with stimulation in the posteroventral pallidum only the dyskinesia score is significantly improved. The slight improvements in the off state, in a limited number of cases, are not significant. The most interesting phenomenon in the on state is the initiation of freezing episodes depending on the stimulation intensity. To our knowledge, this has not been reported previously. Therefore, the idea of replacing a lesioning procedure with an augmentative procedure such as in VIM stimulation would not seem reasonable based on these results. Given the high costs of bilateral implants and the patient’s life-long dependence on electronic devices, even the low morbidity associated with pallidal stimulation does not justify this procedure in our opinion. The motor subscore of the UPDRS is improved 30 to 72% by pallidotomy, the activities of daily living score in the off state is improved by 30 to 60%, and dyskinesias in the on state are improved by 90% according to the dyskinesia scale. Although the results achieved by Mundinger and Riechert are difficult to compare because of the different kinds of examination scores, they were able to abolish or markedly decrease (by 89%) rigidity in 247 patients undergoing pallidotomy. They stated that akinesia was only slightly improved. The complication rate of unilateral pallidotomy ranges from 0 to 14%. The most serious complications include hemiparesis, apraxia, dysarthria, and hemianopsia. No deaths are described in these studies. We had no operative morbidity in our six cases. With an increase in stimulation intensity, freezing occurred in all patients, and two patients developed dystonic movements of the mouth and dysarthria, probably because of stimulation of the genu capsulae internae with higher intensities. All of these side effects were reversible when the stimulation intensity was turned down.

The neuropsychological findings demonstrated inconclusive results regarding verbal memory (logical memory from the Wechsler Memory Scale: two improvements, two deteriorations, two unchanged). Nonverbal memory was improved in all but one patient (Benton Visual Retention test). The Stroop test, a marker for concentration and selective attention, showed no changes in four patients, deterioration in one, and improvement in one postsurgically. Verbal fluency was unchanged in five patients and improved in one.

Target Localization

We used the same target as that described by Laitinen and others for posteroventral pallidotomy. The depth below the anterior commissure to posterior commissure line was determined by the optic response to micro- and macrostimulation. Magnetic resonance imaging was used for target localization. Extensive phantom tests
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with different phantoms, different sequences, localizers, and frames were performed to determine the amount of distortion, which was in the range of 1 to 2 mm at the localizers, depending on the slice orientation. Although many European centers still use ventriculography alone or in conjunction with MR imaging, recent surveys in the United States reveal that most centers use MR imaging alone. One of the advantages of MR studies is the possibility of direct imaging of the target area and the delineation of structures such as the internal capsule and the optic tract, which should be avoided. Intraoperative neurophysiological testing is of the utmost importance to obtain the best clinical results. Postoperative MR imaging confirmed the electrode position in each of our cases (Figs. 5 and 6).

Alternative Stimulation Sites

In contrast to minor improvements in the off state but marked reduction in dyskinesias obtained with pallidal stimulation, stimulation at other sites, especially the subthalamic nucleus (STN), seems to relieve more symptoms of the off state. Based on studies in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine–treated monkeys the role of the STN as the driving force of the GPi has been established. As part of the so-called indirect pathway, the STN is under the inhibitory influence of the globus pallidus externus (GPe) and contains excitatory projection neurons to the GPi. In PD a loss of neurons in the dopamine-containing pathways leads to an activation of striatal output to the GPe (and an inhibition of striatal outflow to GPi and substantia nigra pars reticulata [SNr]), via gamma-aminobutyric acid (GABAergic) inhibitory fibers. This creates a disinhibition of the STN, which in turn leads to excitation of the GPe. Therefore, changes in the striatal outflow via the indirect and direct pathways increase the GABAergic activity of the GPe and SNr, resulting in inhibition of thalamocortical neurons. More recently the STN has been considered an integrative nucleus in the basal ganglia circuitry and a relay nucleus with strong cortical input, which could also lead to increased neural activity after dopamine depletion. A direct influence of dopamine depletion could also be possible because of the direct connection between the substantia nigra pars compacta (SNC) and the STN. The subthalamic function dependence on depletion might be reflected by the fact that subthalamic lesions in nonparkinsonian patients create ballistic, hyperkinetic movements, whereas therapeutic lesioning or current-induced blockade is considered to be helpful in patients with PD. Very high frequency stimulation of the STN demonstrated encouraging results with significant improvement in the motor performance (UPDRS Part III) and the activities of daily living (UPDRS Part II: ADL). Although long-term follow-up studies, such as those for VIM stimulation, are still lacking, the initial clinical results have been replicated in a considerable number of patients (F Alesch and P Limousin, personal communication, 1996). Therefore bilateral STN stimulation seems to be a more appropriate substitute or alternative to pallidotomy than pallidal stimulation. Only a very restricted group of patients with severe levodopa-induced dyskinesias and minor problems in the off state should be considered candidates for pallidal stimulation.

The question also arises as to whether other parts of the pallidum are more appropriate targets, as suggested in recent case reports. The role of the GPe and its connections to the GPi, STN, SNr, and reticular thalamic nucleus also must be redefined. The GPe might play an important role in influencing different basal ganglia output structures, not only the STN. In particular the connections to the reticular thalamic nucleus are of interest, because disinhibiting thalamic VA/VL cells, which are in the resting state under tonic inhibition by GPi and SNr, is a prerequisite for the initiation of movement. This could
be one of the reasons for the different outcomes between stimulation and lesioning of the pallidum. In many patients in whom lesioning has been performed, parts of the GPe may also have been inadvertently lesioned, whereas stimulation is usually restricted to GPi. More recently the lesions have been placed according to microelectrode recordings, resulting in several small lesions restricted to the GPi.

The pedunculopontine nucleus (PPN) is considered a major outflow target for GABAergic pallidal fibers. In cats the PPN is located in a region called the mesencephalic locomotor region, which induces locomotion after stimulation in the decerebrated animal. In contrast, 90% of the PPN in humans consists of cholinergic neurons with mainly ascending projections, with terminations in STN, pallidum, and SNr. The descending projections to the spinal cord, in contrast to those of rodents, are rather scarce in humans. Therefore, this nucleus cannot be considered a major descending outflow structure of the basal ganglia but rather an integrative part of basal ganglia loops. Stimulation in the PPN during stereotactic surgery in humans did not produce any motor changes but instead paniclike reactions.

**Conclusions**

Bilateral pallidal stimulation, although a very attractive augmentative procedure in contrast to pallidotomy, does not provide the same results in improving the on and off symptoms in patients with PD. This has been demonstrated in a small number of patients and warrants further investigation. Considering bilateral procedures and noting the side effects of bilateral lesioning, bilateral stimulation in the ventral intermediate thalamic nucleus of the thalamus as a treatment of movement disorders.

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Manuscript received January 15, 1997.
Accepted in final form June 10, 1997.
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