Stereotactic Pallidotomy in the Treatment of Parkinson Disease

An Expert Opinion

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The objective of this workshop was to provide recommendations on several issues involving pallidotomy for patients with medically intractable Parkinson disease to physicians, patients, and other health care providers. An international consortium of experts in neurology, neurosurgery, and neurophysiology who had extensive experience with pallidotomy were invited to the workshop. Participants were sent background materials from the scientific literature for review-based participant recommendations. A proposed agenda was circulated to all participants before the workshop, and the final agenda was based on their recommendations. Topics were introduced at the workshop by members of the organizing committee, followed by extensive group discussion. A draft of a consensus statement, based on the previous day’s discussion, was circulated and further modifications were made. The final statement was agreed on by all members. The conclusions of the participants were: (1) Pallidotomy should be performed only at centers that have a team of physicians with substantial expertise and experience in the field. (2) Patients with disabling idiopathic Parkinson disease, without dementia, and who have exhausted medical therapy should be considered for pallidotomy. (3) All patients should be examined by means of standardized rating scales both preoperatively and postoperatively to ensure quality of care at each center. (4) Symptoms that respond best to pallidotomy include medication-induced dyskinesias, rigidity, and tremor, while balance, gait disorders, and hypophonia are generally less responsive to surgery. Benefits of pallidotomy appear to be long lasting. (5) Each institution’s complication rate should be discussed before surgery.

Surgical operations in the basal ganglia for idiopathic Parkinson disease (PD) were described as early as 1940.1 Surgical approaches have concentrated on ablation of small regions of the basal ganglia and thalamus, implantation of dopamine-secreting cells, and deep-brain electrical stimulation. In early studies, stereotactic lesions in the globus pallidus appeared to improve rigidity, but inconsistent results were reported for the relief of tremor and bradykinesia.2 Even though Svennilson et al3 reported consistent benefit for tremor, rigidity, and bradykinesia with a more posterior, ventral, and lateral target, many neurosurgeons moved to the thalamus because of unpredictable outcomes with pallidotomy. Thalamotomy was found to result in long-lasting improvement in tremor and rigidity but not bradykinesia.4 Surgical approaches for the treatment of PD became less frequent when levodopa therapy became available in the late 1960s. Despite advances in the medical management of PD, however, patients often develop severe disabling medication-induced dyskinesias and motor fluctuations. These persistent problems led to further investigations of a role for stereotactic surgery in the treatment of PD and other movement disorders.5

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Several centers around the world have applied magnetic resonance (MR) imaging, electrophysiological testing, and modern stereotactic neurosurgical techniques to improve the outcome of ablative therapy and reduce the rate of complications. The efficacy of stereotactic pallidotomy in treating patients with medically intractable PD is supported by several recent reports (Table). None of these studies was double-blinded or placebo controlled, they had a small population size, and there were potential management biases; therefore, definitive conclusions regarding indications, extent of improvement, and complications cannot be drawn. Recently, a preliminary report of a randomized study has been presented, and results from this study also support the efficacy of the procedure. The ethics and costs of sham surgery make blinded trials extremely difficult. Although more than 390 pallidotomies are represented in the literature, many more operations have been performed but not formally reported. Therefore, a workshop was conducted to bring together many of the leading neurologists and neurosurgeons in the field to address many issues involving the procedure that remain unresolved. A consensus was reached on recommendations for patient selection, institutional requirements, preoperative and postoperative evaluation, lesion targeting, and anticipated benefits of the procedure. Below are the recommendations agreed on at this workshop.

RATIONALE OF PALLIDOTOMY

Early surgical targets in treating patients with PD were discovered serendipitously. The current model of basal ganglia circuitry and dysfunction in disease at least partially predicts the therapeutic effects of pallidotomy. In general, increased inhibitory output from the internal segment of the globus pallidus (GPi) is associated with parkinsonism, whereas decreased output is associated with dyskinesias. Loss of striatal dopamine in the case of PD leads to overactivity of the indirect pathway (excitatory) and underactivity of the direct pathway (inhibitory) to the GPi. This ultimately leads to excessive inhibition of the thalamus by the GPi. Lesions of the posteroverentral aspects of the pallidum presumably interfere with the excessive pallidal inhibition of the thalamus and brainstem. This simple model does not predict, however, the dramatic effect pallidotomy has on drug-induced dyskinesias. This and other shortcomings of the current models have been discussed in several recent reviews.

METHODS

Panel Selection

Participants of the panel were invited on the basis of their expertise in the area of pallidotomy and basal ganglia function. Ninety percent of those invited attended the workshop or sent a representative from their institution. Their expertise was based on having at least 1 peer-reviewed publication in the field and/or practice at centers that perform a high volume of procedures. Approximately an equal number of neurologists and neurosurgeons were invited. All opinions in this statement represent those who attended the workshop (13 neurologists, 12 neurosurgeons, and 3 basic scientists).

We distributed a proposed agenda and several reprints to all participants before the meeting. Participants were encouraged to suggest changes to the agenda and additional articles. These additional materials were then distributed in a second mailing.

Meeting

On arrival, all participants received a packet containing the final agenda and names of all participants. Topics were introduced by one of us (J.M.B., A.D., or M.R.D.), and experts in that topic were asked to present their views. Discussion was then opened to the floor, allowing all participants to contribute. Detailed notes of the discussions were taken by 2 individuals, and the entire meeting was tape recorded. Before the end of the meeting, a preliminary statement was prepared and distributed on the last day. Each issue was discussed again. The final statement was prepared by us on the basis of this final discussion, and the manuscript was sent to all participants for their final comments and approval.

RECOMMENDED INSTITUTIONAL REQUIREMENTS

Stereotactic pallidotomy should be performed at centers with a team of physicians and support staff. All patients should be examined and medically treated by a neurologist with expertise in diagnosing and caring for patients with PD. It is recommended that the neurosurgeon be trained in stereotactic and functional neurosurgery and the institution be well equipped. Adequate facilities should provide high-resolution MR imaging (with appropriate software) and full stereotactic capabilities. As with many surgical procedures, experience is important in obtaining optimal outcomes. It is therefore recommended that a pallidotomy center perform at least 25 procedures per year and have an established track record.

PATIENT SELECTION

There was consensus in the panel that the following criteria be used to select patients for pallidotomy.

Inclusion Criteria

Patients with idiopathic PD who have exhausted medical therapy to control disabling symptoms should be considered as possible candidates for pallidotomy. The criteria for the diagnosis of PD requires (1) the presence of at least 2 of the cardinal features of PD (rest tremor, rigidity, and bradykinesia); (2) clear response to levodopa (patients should be examined in both the “on” and “off” states); (3) no evidence of other causes (encephalitis, exposure to toxins, recent exposure to neuroleptics, head trauma, or relevant vascular disease); (4) lack of cerebellar ataxia, vertical gaze palsy, and pronounced autonomic features; and (5) MR images without lacunar infarcts that are thought to be causative of the parkinsonism, normal-pressure
<table>
<thead>
<tr>
<th>Source, y</th>
<th>No.</th>
<th>Age Range, y</th>
<th>Design</th>
<th>Mi</th>
<th>Follow-up</th>
<th>Results</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laitinen et al,6 1992</td>
<td>38</td>
<td>30-80</td>
<td>Open</td>
<td>No</td>
<td>2-71 mo</td>
<td>4-point scale, 81% good to excellent</td>
<td>14% VFD, 1 of these also with transient facial weakness</td>
</tr>
<tr>
<td>Lozano et al,7 1995</td>
<td>14</td>
<td>44-71</td>
<td>Open</td>
<td>Yes</td>
<td>1 wk, 3 mo, and 6 mo</td>
<td>CAPIT: 15%-33% improvement &quot;off&quot;; 92% reduction in dyskinesia &quot;on&quot;</td>
<td>21% Transient facial weakness</td>
</tr>
<tr>
<td>Dogali et al,8 1995</td>
<td>18/7</td>
<td>42-79</td>
<td>Nonrandom controls</td>
<td>No</td>
<td>3, 6, 9, and 12 mo</td>
<td>CAPIT: 38%-65% improvement &quot;off&quot;; significant &quot;on&quot; and dyskinesia</td>
<td>No complications</td>
</tr>
<tr>
<td>Iacono et al,9 1995</td>
<td>58/66</td>
<td>31-80</td>
<td>Open</td>
<td>Some</td>
<td>4.5 mo (mean)</td>
<td>UPDRS, H&amp;Y &quot;on&quot;: 50%-70% improvement</td>
<td>2.4% Transient, 1.6% permanent hemiparesis; 1.6% permanent and &lt;1% transient hemianopsia</td>
</tr>
<tr>
<td>Sutton et al,10 1995</td>
<td>5</td>
<td>64-75</td>
<td>Open</td>
<td>No</td>
<td>2, 4, and 8 wk</td>
<td>UPDRS, H&amp;Y, S&amp;E: improvement in dyskinesia only</td>
<td>40% Transient facial weakness, 40% VFD, 40% depression, 20% worsened speech and swallowing</td>
</tr>
<tr>
<td>Baron et al,11 1996</td>
<td>15</td>
<td>38-71</td>
<td>Open</td>
<td>Yes</td>
<td>3, 6, and 12 mo</td>
<td>CAPIT, S&amp;E: 30% improvement, dramatic reduction in dyskinesias, no neuropsychological deficits</td>
<td>7% Transient and permanent dysarthria, 7% VFD, several transient confusion and hemiparesis, 13% asymptomatic hemorrhages</td>
</tr>
<tr>
<td>Masterman et al,12 1998</td>
<td>32</td>
<td>34-82</td>
<td>Open</td>
<td>Some</td>
<td>3-6 mo</td>
<td>UPDRS: 83% of patients improved 22%-61%; H&amp;Y and S&amp;E: improved; posturography: improved balance, no neuropsychological deficits</td>
<td>3% Transient facial weakness, 13% transient confusion</td>
</tr>
<tr>
<td>Johansson et al,13 1997</td>
<td>22</td>
<td>43-78</td>
<td>Open</td>
<td>No</td>
<td>4 and 12 mo</td>
<td>UPDRS: improved; timed motor: ND; movement analysis: ND</td>
<td>9% Transient confusion or dysarthria, 4.5% VFD</td>
</tr>
<tr>
<td>Krauss et al,14 1997</td>
<td>36</td>
<td>40-75</td>
<td>Open</td>
<td>Yes</td>
<td>6 mo</td>
<td>UPDRS motor: improved by 43% when &quot;off&quot;; ADL: improved by 42% when &quot;off&quot;</td>
<td>14% Transient effects, none persistent</td>
</tr>
<tr>
<td>Lang et al,15 1997</td>
<td>40</td>
<td>44-72</td>
<td>Open</td>
<td>Yes</td>
<td>6, 12, and some at 24 mo</td>
<td>UPDRS: motor &quot;off&quot; improved 28%, dyskinesia 82%; most contralateral improvements were long-lasting</td>
<td>35% With ≥1 persistent adverse effect</td>
</tr>
<tr>
<td>Utti et al,16 1997</td>
<td>20</td>
<td>49-78</td>
<td>Open</td>
<td>Some</td>
<td>3 mo</td>
<td>UPDRS: total improved 22%, little change in neuropsychological findings</td>
<td>20% Transient confusion or incontinence, none persistent</td>
</tr>
<tr>
<td>Samuel et al,17 1998</td>
<td>26</td>
<td>40-72</td>
<td>Open</td>
<td>Yes</td>
<td>3 and some at 12 mo</td>
<td>UPDRS: motor &quot;off&quot; improved 27%; dyskinesia improved 67%</td>
<td>2 Deaths (7.7%), 15% major and 39% minor complications</td>
</tr>
<tr>
<td>Vitec et al,18 1998</td>
<td>27</td>
<td>NS</td>
<td>Randomized (surgical vs medical)</td>
<td>Yes</td>
<td>6 mo</td>
<td>Surgical treatment: UPDRS 33% improved, S&amp;E &quot;off&quot; improved 39%; medical treatment: UPDRS 5% worse</td>
<td>NS</td>
</tr>
<tr>
<td>Kishore et al,19 1997</td>
<td>24</td>
<td>37-74</td>
<td>Open</td>
<td>No</td>
<td>3-12 mo</td>
<td>UPDRS: total &quot;off&quot; improved 38%, total &quot;on&quot; no change; dyskinesia improved 56%</td>
<td>4% Hemorrhage at 2 wk (died), 13% transient hemiparesis, 13% asymptomatic VFD, 4% persistent facial paresis</td>
</tr>
</tbody>
</table>

* Mi indicates microelectrode recordings; open, open enrollment; VFD, visual field defects; CAPIT, Core Assessment Program for Intracerebral Transplantation; UPDRS, United Parkinson's Disease Rating Scale; H&Y, Hoehn and Yahr Staging Scale; S&E, Schwab and England Scale; ND, not done; ADL, activities of daily living; and NS, not stated.
† Pallidotomy/control.
‡ Unilateral/bilateral.
hydrocephalus, and marked cerebellar and/or brainstem atrophy.

An appropriate surgical candidate should have persistent disability despite optimal medical management. The degree of disability depends on the individual and the nature of the disability. It was the general opinion at the workshop that no maximum or minimum age or stage of the disease should preclude consideration for pallidotomy. This opinion was based on the fact that effective pallidotomies have been safely performed on patients from 30 to 82 years of age, although some participants suggested that younger patients obtain better results from pallidotomy than older patients. Because several disorders can easily be mistaken for PD and the management of advanced PD can be difficult, the panel believed that patient evaluations and treatment should be performed by a neurologist with expertise in movement disorders.

Exclusion Criteria
Patients with Parkinson-plus syndromes (multiplesystem atrophy, progressive supranuclear palsy, vascular parkinsonism, etc) should not be considered for pallidotomy, since it has been found to be ineffective in these disorders. Patients with dementia should not be considered for pallidotomy because the cognitive status of the patient may worsen as a result of the procedure (see “Cognitive Screening” section, below). Patients with medical conditions that add unacceptable surgical risk or have MR imaging evidence of other intracranial disease are poor candidates for this procedure. Substantial psychiatric disorders, including severe depression and psychosis, should exclude patients from pallidotomy, although patients with depression can be treated and then considered for surgery.

PREOPERATIVE AND POSTOPERATIVE EVALUATIONS

Standardized outcome analysis is extremely important in ensuring quality of care at each center, especially as they are becoming established. The participants believed that all patients should be examined in the on and off states both preoperatively and postoperatively by means of the United Parkinson’s Disease Rating Scale,24 the Hoehn and Yahr Staging Scale,25 and the Schwab and England activities of daily living scale.26 It is also recommended that a measure of quality of life be used, although no one scale has yet been universally accepted.27,28 The Parkinson’s Disease Study Group is developing a quality-of-life rating system for patients with PD (the PDQUALW), and the panel believed that it should also be considered when available. Positron emission tomography may have some usefulness in predicting outcomes in some patients,29 but the participants thought that further investigation is necessary before its use can be endorsed.

COGNITIVE SCREENING

The cognitive status of patients with PD does not appear to change markedly after pallidotomy if there are no major preexisting cognitive deficits.11,12,16,30 Although this is not firmly established. Since patients with dementia may worsen after pallidotomy, the panel believed that it is imperative to perform an adequate preoperative cognitive evaluation on all patients. In general, patients who fulfill criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,31 for dementia or have a substantial isolated amnestic syndrome should be excluded. Formal neuropsychological testing may not be necessary for all patients. Masterman et al12,30 found a 4-part cognitive battery adequate as a first screening tool to identify those who should undergo more formalized testing. This battery includes a Mini-Mental State Examination,32 memory problem checklist, Superspan Memory Test,33 and a behavioral assessment (ie, Neuropsychiatric Inventory,34 Beck Depression Inventory,35 or Hamilton Depression Scale36). Verification of this or other preoperative cognitive evaluation is required before any one evaluation could be endorsed by the panel.

PREOPERATIVE COUNSELING

Several issues should be discussed with all patients before surgery. It should be made clear that pallidotomy treats some symptoms better than others and that patients should have realistic expectations. In general, levodopa-induced dyskinesias and dystonias (especially “on-time” painful dystonias) and motor fluctuations are highly responsive to pallidotomy in the majority of patients. Rigidity, bradykinesia or akinesia, tremor, and facial masking are also clearly responsive to surgery. Less and more variably responsive symptoms include gait disorders (festination gait, turning, and step size), posture, balance, hypophonia, micrographia, and “off-time” freezing. Non-responsive symptoms include autonomic dysfunction, sphincteric signs (ie, incontinence), drooling and swallowing difficulties, and cognitive impairment. On-period disability that is unrelated to dyskinesias rarely improves in response to pallidotomy. Benefits from surgery appear to be long lasting,15 with 1 report demonstrating improvements up to 4 years.37 Detailed studies on larger series are necessary to fully define long-term results of pallidotomy.

In general, surgical complications from pallidotomy are infrequent, but substantial morbidity and mortality have been reported (Table). In the published literature, 3.6% (15/416) of all patients sustained a permanent visual field defect, 1.4% (6/416) sustained a permanent hemiparesis, and several patients had transient symptoms.38 In 1 report, 3 delayed internal capsule infarcts occurred 13 to 117 days after pallidotomy, all in patients with known vascular risks.39 Three deaths have been reported in the modern literature,37,39 2 of them occurring in their early cases. In fact, most centers reported that the majority of their complications occurred early in their series, and the rate fell with experience. For this reason, the panel recommends that centers have a considerable amount of experience in performing pallidotomies (see recommended institutional requirements) and that patients discuss with their physician the complication rate for each center. Potential surgical patients should also understand that they may be excluded from future...
medical and surgical trials and that pallidotomy may alter the effectiveness of future therapies.

**BILATERAL PALLIDOTOMY**

There are much fewer data available evaluating the benefits and complications of bilateral pallidotomy. There have been a few reports of speech and swallowing difficulties after unilateral pallidotomy, but there is little evidence that bilateral surgery poses additional cognitive risks after well-placed lesions are administered. Many of the participants at the workshop have successfully performed staged bilateral pallidotomies with good results, although some complications have occurred. It is unclear whether these complications reflect poorly placed lesions or the risk of adverse events is inherently greater when a second procedure is performed (ie, more than twice the risk of unilateral pallidotomy). Since unilateral pallidotomy often has bilateral benefits and bilateral surgery may pose additional risks, the panel believed that bilateral pallidotomy should be considered only as a staged procedure with at least a 6-month interval between surgeries. Indications for a second pallidotomy include severe drug-induced symptoms on the side not operated on and a good response to the previous surgery. Patients with speech or swallowing difficulties (by history and examination) or cognitive decline after the first procedure should be excluded from a second operation.

**SURGICAL CONSIDERATIONS**

Before surgery, all antiplatelet agents (aspirin, noncorticosteroidal anti-inflammatory agents, etc) should be discontinued for at least 2 weeks. The blood pressure should be well controlled preoperatively, postoperatively, and intraoperatively to avoid intracerebral hemorrhage. Anti-parkinson medications should be limited the day of surgery to achieve a modest off state but avoid dangerous and uncomfortable severe rigidity, akinesia, and off dystonia.

**TARGET SELECTION**

There is some variation between centers as to where lesions are targeted. Benefits from surgery have been shown to result in both patients and animal models from lesions confined to the caudal (sensorimotor) portion of the globus pallidus pars interna (GPI). Lesions directed to the posteroventral pallidum that include both GPI and external segment of the globus pallidus (GPe) have been reported to be effective in patients. Further studies are necessary to better define ideal lesion placement. The techniques used to determine the target coordinates varied at different centers, but most used MR imaging-guided stereotaxis. Computed tomography-guided targeting has also been reported to be relatively safe and effective. Since both MR imaging- and computed tomography-determined targets can be inaccurate and since the target cannot be adequately determined on anatomical grounds alone, there is general agreement on the need for electrophysiological guidance (stimulation) and intraoperative examination. For this reason, it is strongly recommended that radiosurgery (eg, gamma knife) not be used to perform pallidotomy. Consensus regarding the added value of microelectrode mapping was not reached because of a lack of data. Safe and effective pallidotomies have been performed both with and without microelectrode recordings (Table). The panel believed that there is no evidence that microelectrode mapping is associated with additional surgical complications (eg, hemorrhage, infection). Microelectrode mapping requires both special equipment and experienced personnel and should be performed only at centers with expertise in this technique.

Many centers perform postoperative MR imaging or computed tomography to determine if a hemorrhage has occurred. It was generally agreed that these images offer little in determining lesion placement at conventional resolution.

**CONCLUSIONS**

In our deliberations, we reached consensus on several issues involving pallidotomy. It is recommended that pallidotomy be performed at centers that have a team of experts to ensure that patients are adequately examined and medically treated before surgery is considered. Neurosurgeons should be trained in stereotactic and functional surgery, be well equipped, and have an established track record. Only patients with idiopathic PD and persistent disability who have exhausted medical therapy should be considered for pallidotomy. Good candidates should not have dementia or other medical conditions that would add substantial surgical risk. Standardized rating scales are recommended to ensure quality of care at each center. Several issues should be discussed with all
patients before surgery so they will have realistic expectations of potential benefits and surgical risks. It was generally agreed that contralateral medication-induced dyskinesias, rigidity, and tremor are the most responsive symptoms, while gait disorders, hypophonia, balance, and freezing are less or more variably responsive symptoms. Nonresponsive symptoms include autonomic dysfunction, incontinence, drooling and swallowing difficulties, and cognitive impairment. Surgical complications are generally few, but the complication rate at each center should be discussed. There was less agreement on bilateral pallidotomy, since much less information is available, but it may pose an increased risk of speech and swallowing difficulties. It was agreed that if bilateral procedures were to be performed, they should be staged. Consensus was reached on the general region where the lesion should be placed (posteroventral pallidum including the GPi), but the panel believed that insufficient data were available to make more specific recommendations.

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REFERENCES