

Pallidotomy in Parkinson's disease

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Findings by SBU Alert

Neurosurgery is not widely used to complement pharmacological treatment of Parkinson's disease. Pallidotomy, a procedure involving heating of malfunctioning brain tissue with an electrode, is the method which has received greatest attention during the 1990s. Several uncontrolled studies have shown that pallidotomy reduces symptoms such as hyperkinesia (involuntary movement), rigidity (stiffness), dystonia (painful muscle cramps), tremors (shakiness), and akinesia (poverty of movement), in that order.

Based on the studies reviewed, SBU Alert has found moderate* evidence to support the short-term effects of the method on patient symptoms. However, poor* evidence has been presented yet regarding the duration of these effects and their importance on the patient's quality of life.

Pallidotomy should be performed only in conjunction with scientific studies until more knowledge is acquired on patient benefits and reliable data demonstrates the relationship between costs and benefits.

*This assessment by SBU Alert uses a 4-point scale to grade the quality and evidence of the scientific documentation. The grades indicate: (1) good, (2) moderate, (3) poor, or (4) no scientific evidence on the subject. For further information please see "Grading of evidence".

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Technology

Parkinson's disease is a progressive, degenerative disorder resulting from loss of dopamine-producing cells. Dopamine regulates and modulates movement in the body. The disease cannot be cured, but many of the symptoms can be effectively ameliorated by medications containing L-dopa (which is converted to dopamine in the brain) and so-called dopamine agonists and inhibitors of Dopamine degradation. Treatment frequently begins to fail after 5 to 10 years, and many patients experience L-dopa-specific side effects, ie, hyperkinesia and dyskinesia (involuntary movement).

During the past decade, a neurosurgical intervention called pallidotomy (electrical "cauterization" or radiofrequency coagulation in parts of the globus pallidus at the base of the brain) has been shown to have favorable effects on the disease by eliminating dyskinesias while simultaneously and to varying degrees, ameliorating other symptoms (rigidity, painful cramps, tremors, and akinesia).

Pallidotomy can enable some patients to maintain or increase the L-dopa dose as dictated by the disease symptoms. The method involves using stereotactic (three-dimensional) technology to guide a thin electrode to a specific part of the brain, use electrical stimulation to see that the electrode is positioned correctly, and then heat the tissue around the electrode point to interrupt diseased nerve pathways. The purpose of pallidotomy is to ameliorate symptoms; the procedure does not stop the course of disease and does not eliminate the need for medication. The method itself is continually evolving. Advancements focus on further specifying the tissue volume to be destroyed and its location.

Pallidotomy is always performed under local anesthesia, hence enabling the surgeon to monitor effects and potential side effects while operating on an alert patient.

Target group

An estimated 20 000 people in Sweden have Parkinson's disease. The disease affects mainly people over the age of 50 years. A study from Great Britain shows that approximately 10 per cent of all patients with Parkinson's disease do not respond well to medical treatment. The percentage of this group who would benefit from pallidotomy is yet unknown. Furthermore, several new drugs are being assessed as single therapy or as a complement to other therapy. Further dose adjustments are tested as new drugs are introduced for treatment.

The most suitable patients for pallidotomy are those who suffer from severe, L-dopa-induced symptoms involving dyskinesias or "on-off" effects where the "off" periods are characterized by severe muscle stiffness or muscle pain with or without tremors.

Relation to other technology

Pallidotomy has been developed in parallel with other stereotactic interventions in the brain. At one time, this intervention was neglected since it was overshadowed by thalamotomy when that method gained popularity during the 1950s and 1960s, and by L-dopa when the drug was introduced in the late 1960s. Recently, it was shown that thalamotomy is associated with relatively severe side effects, limiting the benefits of the treatment.

During the mid 1980s, pallidotomy experienced a renaissance in that posteroventral pallidotomy was reintroduced and further developed. At approximately the same time thalamus stimulation (chronic electrical stimulation of the thalamus) was promoted, and this method has largely replaced thalamotomy. Among the surgical methods used internationally, pallidotomy holds on to its leading position.

Patient benefits

More than 170 reports on various aspects of pallidotomy have been published since 1992. As is the case with thalamotomy and other surgical methods, no prospective randomized studies have compared pallidotomy with best medical treatment. Such a study was started in Atlanta, but reportedly was terminated after 6 months. It was viewed as unethical to continue the study after 6 months since the

results in patients receiving the operation were superior to the results in those not receiving it, particularly concerning the amelioration of hyperkinesia (Roy Bakay, Atlanta).

We found several detailed, although small, prospective studies with postsurgical followup periods ranging from 6 months to 4 years [1,6,8,12,13,19,22,24,25]. Common to most of these studies were the relatively short followup periods (since the method was relatively new) and the relatively small numbers of patients. Although one cannot ignore the possibility of placebo effects, there are data to show a positive and relatively long-term effect of pallidotomy on several disease symptoms, mainly dyskinesias, followed by dystonias, rigidity, tremors, and akinesia.

The studies provide some support for the following conclusions:

- Pallidotomy eliminates or ameliorates pronounced and prolonged dyskinesias (involuntary movement induced by L-dopa).
- Pallidotomy substantially ameliorates painful cramps, dystonia, which has also led toward using the procedure for non-Parkinsonian dystonia symptoms [21].
- Rigidity is ameliorated to approximately the same degree as dystonia.
- Tremors are ameliorated in approximately 60 per cent of the patients. However, this effect is not equally as noticeable, and probably not as prolonged, as following thalamotomy or thalamus stimulation.
- Akinesia is ameliorated by pallidotomy, but here the effects are not as obvious. Some studies show marginal or insignificant effects [12], while others suggest that akinesia is ameliorated in up to 50 per cent of the cases [6]. Differences may be the result of how patients are assessed and what is included in the concept of akinesia. For example, the inability to start walking, "gait freezing", which is one of the most severe forms of akinesia, shows slight improvement following pallidotomy, while the swinging the arms while walking is largely restored.

The so-called on-off phenomenon which is common in advanced Parkinson's disease is ameliorated in a large share of cases. The milder symptoms include less fluctuation between on and off, and patients demonstrate a more "even level" in their mobility throughout the day. In cases where "on-off" symptoms persist, the "on" periods are longer and nearly free from dyskinesias, while the "off" periods are not as deep and not as immobile as prior to the operation.

ADL ability (ability to manage activities of daily living) as measured by a standardized questionnaire shows a varying, although significant, degree of improvement [19].

Other effects of pallidotomy include some weight gain (possibly resulting from a reduction in energy demanding involuntary movements), improved facial expression, (reduction of rigidity), and improved sleep (better ability to turn in bed).

Complications and side effects

Most studies have reported few risks to patients. The first study using modern surgical methods [16] showed that the primary side effect was a vision field defect which occurred in 14 per cent of patients receiving surgery. This complication was virtually eliminated after modification of the surgical method and after MRI replaced CT as the imaging modality [11,17,18].

Stereotactic surgery may result in cerebral hemorrhage. The risk of hemorrhage has been low (less than 1 per cent) in the series of patients receiving surgery with macro-electrodes and macro-stimulating methods, ie, the treatment approach used in Sweden [9]. Series involving micro-electrode methods, requiring more electrode passages in the brain (used mostly in the United States, but also in England and Spain), the risk of hemorrhage was clearly higher [5,20,24,26]. The risk for infection is virtually non-existent.

There is also a risk for destroying tissue in surroundings structures in the pallidum. This can lead to injury in the pathway of nerves that control motion, which can result in weakness to one side of the body, facial weakness, difficulties in articulation, and difficulties in swallowing. The prevalence of these severe complications has also been low (2 per cent to 5 per cent) nationally and internationally, except in a few international reports using micro-electrode technology [20,24,26]. Few of the more prolonged side effects are of a serious nature [19,29]. A joint study from Umeå and Los Angeles including 156 pallidotomy

operations reported the following long-term side effects (persisting more than 6 months after surgery): pronounced fatigue in 1.3 per cent, memory loss in 2.6 per cent, aphonia (loss of voice) in 0.6 per cent, speech difficulties in 2 per cent, weakness in facial or leg muscles in 0.6 per cent, vision field loss in 0.6 per cent, and delayed stroke (ie, blood clot in the brain which appears 3 to 4 weeks following pallidotomy) in 1.3 per cent [11] of the cases.

Costs and cost-effectiveness

The surgical costs depend on the equipment used, the surgical time consumed, the length of hospital stay, and the extent of pre- and postoperative investigations. In 1996, the department in Umeå was reimbursed 48 000 SEK for a pallidotomy operation. All neurosurgery departments in Sweden have the stereotactic instruments required. Pallidotomy also requires preoperative MRI investigation. The surgical procedure itself, which normally takes about 2 hours, is carried out using local anesthesia and does not require general anesthesia or postoperative intensive care. The length of stay following surgery is between 1 and 3 days.

In some cases, surgery contributes toward reducing the need for home services and other care [19].

A British study reports on an estimation of the costs for pallidotomy per quality adjusted life year (QALY) in patients with moderately severe to severe Parkinson's disease [31]. Based on these estimates, the cost for the first 12 months following surgery would fall between 25 000 and 65 000 GBP per QALY. The costs for severe cases range between 16 000 GBP and 27 000 GBP depending on the assumptions regarding the patient's status prior to surgery. If the followup period is extended, the cost per QALY will probably decline.

Structure and organization of health services

The structure or organization of the health services are not affected by the method.

Ethical aspects

The risks associated with this surgery are few and should be weighed against the expected benefits of the intervention. As long as the patient benefits outweigh the potential side effects, the fact that the procedure is irreversible should not cause an ethical problem. In the debate concerning this procedure, the term irreversible is used since a tiny part of the brain is destroyed during surgery. The part of the brain which is targeted for surgery is, however, not healthy. Hence, it often negatively affects other healthy brain functions. Surgery is performed after medication and other medical interventions are no longer effective. It is important for patients to receive adequate information about the operation and participate in the decision.

Diffusion in Sweden

Most procedures have been performed at the Department of Neurosurgery in Umeå, but a few operations were performed on patients at departments in Lund and at the Karolinska Hospital. Also, a few patients received the procedure at Sophiahemmet. In addition to the departments mentioned above, pallidum stimulation is also provided in Göteborg. Thalamus stimulation is offered at all of the clinics mentioned above and in Uppsala, and is being introduced in Linköping. The most recent surgical method, nucleus subthalamus stimulation, is currently offered only in Lund, Göteborg, Umeå, and the Karolinska Hospital in Stockholm. In 1996, approximately 20 pallidotomies were performed (patient registry).

Current evaluation research

Further research and assessment of the method is necessary and is being carried out in various centers in Sweden and throughout the world. Research focuses mainly on the following questions:

What are the long-term effects of pallidotomy on different chronic symptoms and what effect does it have on the course of disease?

What effect does the surgery have on the patient's ability to manage activities of daily living, on the need for assistance, on the disability itself, on quality of life and life satisfaction, and on cognition?

What are the surgical effects in relation to the extent of lesion and its exact position in the various parts of the pallidum [11], or in relation to the surgical method used, macro- or micro-electrode [4], and what are the differences in effects between pallidotomy and pallidum stimulation [28,14]?

Research is also underway to assess a new surgical method involving chronic stimulation of the subthalamic nucleus (STN). Preliminary reports have shown that STN-stimulation is superior to pallidotomy in ameliorating gait-related symptoms in patients with advanced Parkinson's disease [15]. The side effects and the long-term effects of STN stimulation have yet to be assessed.

Experts

Assoc Prof Marwan Hariz, MD PhD, Norrland's University Hospital in Umeå

Reviewers

Olof Corneliusson, MD, Sahlgrenska University Hospital

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