A Review Of Current Surgical Options For The Treatment Of Parkinson's Disease, With Special Emphasis On Deep Brain Stimulation

Parkinson hastalığının cerrahi tedavi secenekleri ve derin beyin stimulasyonu

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Abstract: Surgical treatment of movement disorders, and especially Parkinson's disease, is regaining momentum. Despite all efforts, a significant number of patients who suffer from various types of movement disorders are becoming surgical candidates. Recent advances in medical technology have enabled more precise targeting of deep brain structures, as well as reversible modulation of the neural outputs. Utilization of these technologies in common practice may well expand our options for treating complex movement disorders. Deep brain stimulation is one of these promising advances in stereotactic surgery for movement disorders. This review begins with a historical perspective, and then presents the latest knowledge in this field. The intent was to inform health care providers in neurological sciences about the implications, application, and scope of this technology.

Key words: Deep brain stimulation, movement disorders, Parkinson's disease, stereotaxis, surgery

Özet: Medikal tedavideki tüm yeniliklere rağmen hareket bozukluklarının cerrahi tedavisine gerek duyulan hasta ve yapılan ameliyat sayıları giderek artmaktadır. Parkinson hastalığı cerrahi olarak tedavi edilen hareket bozuklukları içerisinde önemli bir yer tutmaktadır. Tıp teknolojisindeki ilerleme artık derin beyin yapılarının cok daha duyarlılıkla belirlenip hedeflenebilmesine ve buradaki aktivitenin değistirilebilmesine olanak tanımaktadır. Derin beyin stimulasyonu bunların en onemlilerindendir. Bu teknolojilerin yaygın kullanima girmesiyle birlikte stereotaktik hareket bozukluğu cerrahisinin ufku daha da genişlemiştir. Bu derlemede hareket bozukluğu cerrahisinin tarihsel gelişimi, günümüzde yaygın kullanılan cerrahi hedefler, derin beyin stimulasyonu teknolojisi ve uygulamalarının sonuçları gözden geçirilerek bu konularda çalışanlara genel bir görüs kazandırılması amaçlanmıştır.

Anahtar Kelimeler: Cerrahi, derin beyin stimulasyonu, hareket bozukluğu, Parkinson hastalığı, stereotaksi

INTRODUCTION

Movement disorders are a group of neurological conditions that share the common feature of disrupted control of body movements. The best-recognized condition is Parkinson's disease (PD), but others include chorea, dystonia, and tremor due to a variety of causes. These conditions consume a large portion of health care resources, and produce incalculable patient suffering. PD alone costs the United States an estimated $25 billion each year.

Parkinson's disease is a progressive degenerative disease of the basal ganglia. Pathologically, it is characterized by the loss of dopaminergic cells of the substantia nigra (SNr) and pars compacta (23). The major dopaminergic projection from the SNr (nigrostriatal tract) innervates the striatum, although dopaminergic SNr neurons also innervate other regions of the basal ganglia involved in motor control (7,23,31). The cardinal signs of PD are resting tremor, rigidity, bradykinesia, and postural instability. The criteria for the diagnosis of idiopathic PD include at least two of these four cardinal signs, as well as a history of a beneficial response to levodopa (L-dopa).

Historical Background

Surgery on basal ganglia structures was pioneered by Meyers in 1939 (33). As more cases accumulated, Meyers surgically experimented with extirpation or sectioning of various portions of the corpus striatum and related pathways, and showed that tremor could be abolished and rigidity reduced without the production of paresis, spasticity, or dyspraxia (32). Meyers' work was followed by that of Browder and Hamby, whose promising results were accompanied by high mortality (8,21). These high mortality rates with the transventricular approach led Fenelon to develop a free-hand technique for passing an electrode via an anterior subfrontal, a transtemporal, or a transfrontal approach to directly coagulate the ansa lenticularis (15). Guiot and Brion reported a similar technique for direct coagulation of the globus pallidus and ansa lenticularis in 1953 (19). Later, Bertrand was able to surgically isolate the pallidal area (6). Cooper investigated the effects of basal ganglia lesions in movement disorders after an incidental anterior choroidal artery injury, but finally abandoned this technique due to unpredictable results related to anatomical variations in the anterior choroidal artery and its territory (11).

The unacceptable morbidity associated with open surgery for neuroablative procedures motivated researchers to develop safer methods. In 1948, Spiegel and Wycis performed the first stereotactic pallidotomy and thalamotomy on record (43). Soon after that, stereotactic techniques with many variations began to be performed around the world. In 1951, Narabayashi and Okuma tried to treat PD by injecting an oil-wax mixture into the globus pallidus (35). In the same year in Germany, Hassler and Riechert became the first to produce a stereotactic lesion in the ventrolateral nucleus of the thalamus as treatment for PD (22). Mundinger explored the subthalamic nuclei (STN) for the treatment of PD, intentional tremor, and myoclonic-ballistic hyperkinesia (34).

By 1965, it was estimated that more than 25,000 procedures for parkinsonism had been performed worldwide (42). However, with the development of L-dopa treatment, functional neurosurgical procedures declined dramatically after 1968 (12). For decades, the surgical treatment of PD was practically withdrawn from the therapeutic arsenal. In the early 1970s, the follow-up examinations of L-dopa treated patients began to reveal some drawbacks of the substitutive treatment; such as intolerance, loss of efficacy, or even added complications such as abnormal involuntary movements. This marked the beginnings of a renewed need for surgical treatment and better understanding of the anatomy and physiology of the basal ganglia. This need, coupled with improved imaging modalities, the ability to neurophysiologically identify the deep brain structures, and continued progress in surgical technology, led to the resurrection of stereotactic surgery for movement disorders.

Today, the thalamus, globus pallidus, and STN are widely used as effective targets for various movement disorders and for parkinsonism. The advent of deep brain stimulation (DBS) technology enabled us to perform bilateral, reversible, and, perhaps most important, specially tailored interventions for all the above-mentioned targets. These procedures favor a restorative approach to the central nervous system as a means of resolving complex neurological problems.

Mechanism of Action and Surgical Technique for Deep Brain Stimulation

Most patients with movement disorders are treated effectively with medications. A small portion, however, have refractory symptoms. Some of these symptoms can be treated with neurosurgical interventions. Over the years, the safety and efficacy of these procedures have improved with the introduction of stereotaxis, radiofrequency lesioning, non-invasive imaging, and now DBS. Before the introduction of DBS, neurosurgeons could only

destroy the overactive brain regions responsible for movement disorders. The effects of these lesions (usually beneficial but occasionally detrimental) are permanent. Deep brain stimulation is designed to "turn off" these overactive brain regions without destroying them. The immediate advantage of DBS over conventional destructive neurosurgery is that the "lesions" are titratable and, hence, reversible.

It is currently accepted that many of the symptoms of PD are due to overactivity of the inhibitory pallidofugal pathways originating from the internal pallidum (GPi), the GPi being driven in part by overactive STN. The net effect is the inhibition of cortically mediated impulses via the thalamocortical loop (30). Because of the current knowledge of their anatomical relationships and physiological functions, and the ease with which these structures can be accessed through current neurosurgical techniques, the thalamus, Gpi, and STN are suitable targets for both stereotactic lesioning and neuromodulation using DBS.

Theoretically, DBS can influence both neurons in the target structure and fibers passing or bordering that structure (44). It is still not known how the functional suppression of these targets occurs at the cellular level. The effects are frequency-dependent. An effect can be detected with frequencies above 50 Hz, and reaches maximum at 100-200 Hz. High-frequency stimulation has been used as an intraoperative test for optimal targeting for several years (44,48). The implantation of a chronic DBS electrode was initially proposed as an experimental therapeutic procedure (44). When the results were excellent, a pilot study was launched for patients who had undergone previous thalamotomy and required a second operation on the contralateral side (5). When these results were also encouraging, DBS applications were extended to treat other types of movement disorders (3,4,5,16,17,29).

The Hardware

There are three components to the DBS system (ActivaTM, Medtronic Inc., Minneapolis, MN, USA). The first is the DBS lead. The tip of this insulated lead has four platinum/iridium electrodes spaced 0.5 or 1.5 mm apart. These electrodes are placed within the target brain region and are used to deliver the high-frequency stimulation designed to block or disrupt the function of the surrounding brain. An insulated cable, the extension, is tunneled subcutaneously from the DBS lead to its power source. The implantable pulse generator (IPG) (ItrelTM II/III, SoletraTM, Medtronic Inc., Minneapolis, MN, USA) is placed in a subcutaneous pocket below the clavicle and provides both the power for stimulation and the ability to use telemetry to control the stimulation parameters. The final size of the "lesion" is adjusted in the outpatient clinic after surgery by changing these stimulation parameters. The DBS effects can then be tailored to the individual's symptoms, enlarging the "lesion" to increase beneficial effects or reducing its size to avoid a side effect. Figure 1; illustrates the DBS system hardware and the implanted electrode within the thalamus.

The Surgery

There are two parts to any DBS operation: implantation of the DBS lead within the brain and insertion of the IPG. The details of targeting are beyond the scope of this review, but any neurosurgical center with stereotactic experience and appropriate training can perform the operation.

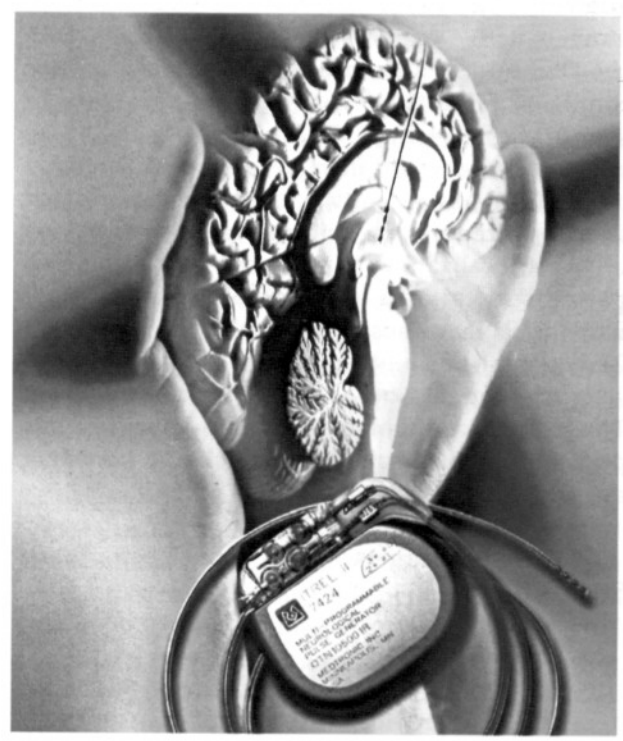

Figure 1: An artist's drawing illustrates the DBS system and the electrode implanted in the thalamus.

Implantation of the DBS Lead:

At the Surgical Centre for Movement Disorders, University of British Columbia, we use a magnetic resonance imaging-compatible head frame (UCLF, Radionics Inc., Burlington, MA, USA) for patients without tremor, and a computed tomography (CT)-compatible frame (CRW, Radionics Inc., Burlington, MA, USA) for those with tremor. Frames are placed using local anesthetic and no sedation is given during the procedure. Patients receive preoperative antibiotics on transfer to the operating room. The hair is shaved over the coronal suture and the scalp is prepared, draped, and infiltrated with local anesthetic. A 14-mm burr hole is drilled in the skull and the dura is opened. The arc system is then attached to the head ring. The brain target area can be localized with either macrostimulation or microelectrode recording. Once the probe has found the target area, it is replaced by the DBS lead under fluoroscopic guidance. The lead is locked in place with a burr hole button and the scalp is temporarily closed.

Insertion of the IPG:

Early in our experience, this portion of the procedure was often performed several days later. Patients with a temporary external extension from the DBS lead to a hand-held trial stimulator were monitored for their response to a variety of stimulation settings. If a good response was confirmed, we would then proceed to implantation of the IPG. More recently, we have been combining the two procedures after intraoperative confirmation of target localization. During insertion of the IPG, patients receive a general anesthetic. Most individuals leave hospital the following day (after 24 hours of antibiotics), although our multiple sclerosis patients occasionally need more time. The procedure involves making a subcutaneous pocket for the IPG below the clavicle and tunneling the extension cable from the scalp to the chest.

Various Targets Used for Deep Brain Stimulation

Thalamic DBS

Thalamotomy for the treatment of tremor was introduced nearly half a century ago (11,22). The introduction of L-dopa treatment and the morbidity related to thalamotomy (particularly with bilateral procedures) made it an unfavorable therapy for PD (24). Even from the earliest days of stereotactic surgery for PD, it was known that acute electrical stimulation at certain brain sites arrested the tremor during stimulation; however, the exact mechanisms of this suppression with DBS are still not well understood (4,44). Deep brain stimulation was not available as a treatment modality until 1980s. In 1987, Benabid and co-workers succeeded in treating parkinsonian patients with drug-resistant tremor using chronic stimulation of the ventrointermediate nucleus of the thalamus (Vim) (6). After achieving successful preliminary results, this group started performing Vim stimulation as a first surgical option, abandoning thalamotomy (4). In time, unilateral DBS became a widely accepted and applicable technique for the treatment of essential and parkinsonian tremor (24,36). Figure 2; shows the thalamic target with respect to the posterior commissure on an axial CT section at the level of the intercommissural line.

Retrospective analysis comparing thalamotomy with thalamic DBS has proven that DBS is as effective as thalamotomy for tremor control, and has fewer potential complications and side effects (28,46,47). It is now widely accepted that bilateral implantation of the DBS electrodes does not carry the potential

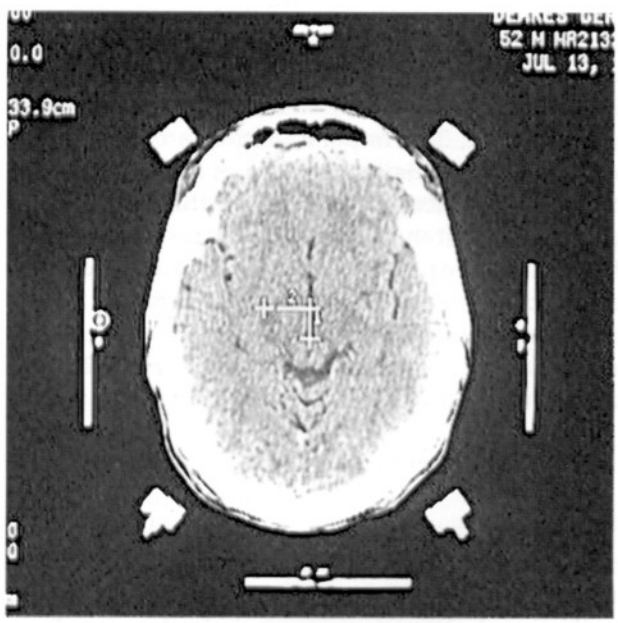

Figure 2: Fig 2: An axial CT scan at the level of anterior and posterior commissures demonstrates the thalamic target point with respect to posterior commissure.

risks of bilateral thalamic lesioning, such as cognitive, memory, language, swallowing, and speech disturbances (4). Dysarthria more often affects patients who have undergone previous contralateral thalamotomy than those who have been treated with bilateral thalamic DBS (4,5). A decrease in L-dopa-induced dyskinesia was reported in some patients (10), but this effect was not found to be significant in other studies (28,48). The improvement of L-dopa-induced dyskinesias after thalamic DBS may be associated with deeper and more medial placement of electrodes (9). A recently published multicenter study shows that thalamic DBS may reduce tremor up to 85% in 12 months of follow-up (28). Both upper and lower limb tremor were reduced, and there was a slight improvement of limb akinesia and rigidity. Speech, postural stability, and gait were not significantly improved, but the activities of daily living (ADL) scores improved as a consequence of reduction in tremor. These results are comparable with those of Vim thalamotomy (24). No published prospective randomized study has yet compared thalamic stimulation and thalamotomy, but one is currently in progress in the Netherlands (41). There are also some recent promising reports about bilateral thalamic DBS for the treatment of isolated head and voice tremors (45).

Pallidal DBS

Pallidotomy was re-popularized after Laitinen's cornerstone work (27). The very encouraging effects of ventroposterolateral pallidotomy on all symptoms of PD led to the introduction of an alternative technique, that of permanent electrostimulation of the pallidum (40). The most dramatic effect of permanent bilateral ventroposterolateral stimulation in PD patients was the disappearance of severe iatrogenic L-dopa-induced dyskinesias (39). In addition, there was clear improvement in akinesia or hypokinesia, as well as rigidity (14,17,38,50). Patients who have undergone unilateral pallidotomy may experience increasing disability due to persistent and progressive signs on the non-operated side. Many neurosurgeons are reluctant to produce bilateral destructive lesions based on the considerable morbidity associated with bilateral thalamotomies. The reversible nature of DBS is preferred to a second destructive procedure. In patients who have undergone prior pallidotomy, contralateral implantation of a DBS electrode is a reasonable alternative to bilateral lesioning (16).

Although there are some controversial reports on the efficacy of bilateral pallidal DBS (49), this variable success may be related to the differential response to stimulation in different parts of the pallidum (2). Stimulation of the lower (posteroventral) pallidum is reported to reduce L-dopa-induced dyskinesia dramatically, but can worsen parkinsonian symptoms (except rigidity) and even block the beneficial effects of L-dopa. Stimulation of the upper (dorsal) pallidum improves parkinsonism, but can induce dyskinesias in the "off" state and worsen them in the "on" state (2). Bilateral pallidal stimulation may be considered an effective and safe alternative for patients who have L-dopa-responsive parkinsonism with untreatable motor fluctuations. In such cases, there is a mean improvement in motor and ADL scores of over 50%, and the patients have no major neuropsychological dysfunction that interferes with daily activities (17).

Subthalamic Nuclei DBS

STN overactivity is a central abnormality in the basal ganglia-thalamocortical circuit in the parkinsonian state. Because the projection from the STN to the GPi is excitatory, one effect of interruption of STN activity should be to correct overactivity in the Gpi, producing an effect similar to pallidotomy. Theoretically, however, the STN may be an even more attractive target than the GPi for alleviation of parkinsonian signs because it affects the function of both basal ganglia output nuclei (SNr and GPi). Thus, interruption of STN activity might potentially alleviate more motor abnormalities than interruption of GPi activity alone. Based on these theoretical considerations, current interest in the STN as a surgical target for PD is increasing (3,18,20,29). STN lesions have been performed in small series of patients with results of considerable improvement in parkinsonism (18), but lesioning of the STN is not preferred as it may induce permanent abnormal involuntary movements like hemiballism and dyskinesia (3). Bilateral lesioning of the STN, which are bordered by the corticobulbar and corticospinal tracts, theoretically has high potential to induce a pseudobulbar syndrome.

The STN have three anatomical characteristics that make them difficult to localize: small dimensions, biconvex lens shape, and obliquity. Because the clinical benefit of STN stimulation is

entirely dependent on the accuracy of target determination, MRI and electrophysiological guidance are used simultaneously for targeting (1). Unilateral STN stimulation mainly affects the contralateral hemibody (13,29). A patient with unilateral STN stimulation will continue to require anti-parkinsonian medication for the ipsilateral hemibody. In advanced-stage disease, unilateral stimulation will not sufficiently improve gait problems, and bilateral contemporaneous STN surgery is preferred.

The effects of high-frequency DBS in the STN were reviewed by Benabid et al. (3). These authors demonstrated that bilateral stimulation of the STN greatly improves off-period symptoms in this group of severely disabled patients. Motor fluctuations were attenuated, and patients with sudden on-off fluctuations before surgery had milder fluctuations thereafter. All patients became independent in most activities of daily living, and medications were decreased to approximately half of the initial dosage after the surgery. The three cardinal symptoms of PD (bradykinesia, rigidity, and tremor) were decreased by stimulation of the STN when patients were off the medication. Off-medication and off-stimulation Unified Parkinson's Disease Rating Scale (UPDRS) motor sub-scale scores were also improved. This could be related either to the microsubthalamotomy effect due to the presence of the stimulating electrode in the STN, or to a long-lasting inhibitory effect of chronic stimulation (29).

A double-blind study done by Kumar and Lozano yielded similar results (26). They reported an approximately 65% reduction in off-period parkinsonism, 40% improvement in on-period parkinsonism, and 85% reduction in levodopa-induced dyskinesias. Although on-period functions were also improved, the authors could not say with certainty that parkinsonian features refractory to the suprathreshold dose of levodopa would respond to STN DBS. When patients who had undergone bilateral STN DBS were compared with those who had undergone bilateral GPi DBS, the STN patients showed considerably greater improvement in off-period parkinsonism. In contrast to most reports on unilateral pallidotomy, bilateral STN DBS patients were also significantly improved in on-periods (26). There are also reports about the effects of GPi and STN stimulation that favor the STN target in young-onset PD with severe L-dopa-induced motor complications (25). STN DBS is also reported to significantly decrease parkinsonian tremor (37).

CONCLUSION

DBS is a powerful new tool in the treatment of movement disorders. It has become a standard treatment for PD and essential tremor, and the applications continue to expand as successful results are reported for other conditions. There is still debate about whether DBS is actually superior to lesioning; however, the ease and benefits associated with adjustable parameters, and the added plus of avoiding another lesion in an already sick brain seem to favor DBS more and more every day. We believe that the most important advantage of DBS is the ability to titrate the effects to suit an individual's changing symptoms.

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