DTM Chan 陳達明
VCT Mok 莫仲棠
WS Poon 潘偉生
KN Hung 洪君毅
XL Zhu 朱獻倫

Surgical management of Parkinson's disease: a critical review

帕金森病的外科處理：評論性回顧

Parkinson's disease is a progressive disabling movement disorder that is characterised by three cardinal symptoms: resting tremor, rigidity, and bradykinesia. Before the availability of effective medical treatment with levodopa and stereotactic neurosurgery, the objective of surgical management was to alleviate symptoms such as tremor at the expense of motor deficits. Levodopa was the first effective medical treatment for Parkinson's disease, and surgical treatment such as stereotactic thalamotomy became obsolete. After one decade of levodopa therapy, however, drug-induced dyskinesia had become a source of additional disability not amenable to medical treatment. Renewed interest in stereotactic functional neurosurgery to manage Parkinson's disease has been seen since the 1980s. Local experience of deep-brain stimulation is presented and discussed in this paper. Deep-brain stimulation of the subthalamic nucleus is an effective treatment for advanced Parkinson's disease, although evidence from randomised control trials is lacking.

帕金森病是一個進行性的運動障礙疾病，它以三個最主要症狀為特徵：靜態震顫，肌張力增加和動作徐緩。在左旋多巴和立體定向神經外科有效治療可用之前，外科處理的目標是減輕諸如震顫的症狀，代價是癱瘓。左旋多巴是用於帕金森病的第一種有效藥物治療，而諸如立體定向的丘腦切開術外科已不被使用。然而，利用左旋多巴治療十年後，藥物引起的肌張力失調成了另一種不可治療的殘疾原。自1980年代以來，人們重新對利用立體定向功能神經外科以處理帕金森病產生興趣。本文介紹和討論了深腦部刺激的本地經驗。儘管下丘腦核的深腦部刺激缺乏隨機化控制試驗證據，但它還是用於嚴重帕金森病的一種有效療法。

Key words:
Electric stimulation;
Globus pallidus/surgery;
Parkinson disease;
Stereotactic techniques;
Subthalamic nuclei/surgery;
Thalamus/surgery

關鍵詞：
電刺激；
蒼白球／外科；
帕金森病；
立體定向技術；
下丘腦核／外科；
丘腦／外科

HKMJ 2001;7:34-9

Division of Neurosurgery, Department of Surgery, The Chinese University of Hong Kong, Prince of Wales Hospitel, Shatin, Hong Kong
DTM Chan, MBChB, FRCS
WS Poon, MBChB, FHKAM (Surgery)
XL Zhu, FRCS, FHKAM (Surgery)
VCT Mok, MBChB, FHKAM (Medicine)
Department of Neurosurgery, The University of Hong Kong, Queen Mary Hospital, Pokfulam, Hong Kong
KN Hung, MB, BS, FHKAM (Surgery)

Correspondence to: Prof WS Poon

Introduction

Parkinson's disease (PD) is a progressive disabling movement disorder that is characterised by three cardinal symptoms: resting tremor, rigidity, and bradykinesia.[1] The prevalence of PD in the general population is reported as being 0.2% to 0.3%. The highest prevalence has been noted in white Caucasians and the lowest in black Africans.[2] Although PD is a neurodegenerative disease of the elderly, 5% to 10% of patients have symptoms before the age of 40 years.[3] It is estimated that 3.4% of the elderly in nursing homes in Hong Kong have the disease.[4] Further increases in the elderly population worldwide will likely result in a steady increase in the prevalence of this disease. Parkinson's disease is associated with an increase in mortality and a reduction of life expectancy in comparison with age-matched controls.[5]

Before the availability of effective medical treatment with levodopa[6] and stereotactic neurosurgery,[7] the objective of surgical management was to alleviate symptoms such as tremor at the expense of motor deficits. This approach involved performing open craniotomy and sectioning of the cerebral cortex,[8] pyramidal tract,[9] and cerebral peduncle.[10] Once the concept of the extrapyramidal system (the basal ganglia, including the striatum, pallidum, subthalamic nucleus, substantia nigra, red nucleus, and dentate nucleus) was described by Spatz in 1927,[11] a more rational experimental approach could be developed.[12] Open craniotomy using an intraventricular approach to resect the basal ganglia (caudate nucleus and putamen) was developed in the 1940s and 1950s with reasonably good results (45% to 62%) in terms of tremor control; however, surgical mortality remained high at 12% to 41%.[13]

In 1953, Cooper[14] described to a postencephalitic patient who underwent pedunculotomy in which the anterior choroidal artery was ligated owing to surgical injury. The resulting ischaemic infarct of the pallidum gave rise to a marked improvement of the tremor. This surgical approach of open craniotomy and pallidotomy subsequently failed to achieve a predictable and favourable outcome, while carrying a high mortality and morbidity risk.[14,15] Stereotactic thermopallidotomy was then favoured because of its minimal invasiveness, but its tremor control remained unpredictable and its effects on akinesia and rigidity were poor.[16,17] Stereotactic thalamotomy had gradually replaced pallidal surgery by the 1960s for tremor control.[18,19]

The impact of the availability of levodopa in the 1960s was enormous.[6] Levodopa was the first effective medical treatment for PD, and it alleviated all three cardinal symptoms—tremor, bradykinesia, and rigidity. Giving levodopa also served as a diagnostic test for the disease, and surgical treatment such as stereotactic thalamotomy became obsolete. After one decade of levodopa therapy, however, drug-induced dyskinesia had become a source of additional disability not amenable to medical treatment. Paradoxically, levodopa-induced dyskinesia has been shown to be effectively controlled by stereotactic pallidotomy of the globus pallidus interna, although its effects on tremor, bradykinesia, and rigidity are variable.[20] Renewed interest in stereotactic functional neurosurgery to manage PD has been seen since the 1980s. In this paper, surgical procedures in the post-levodopa era are critically reviewed and local experience of various techniques presented.

Pathophysiology relevant to surgical management of Parkinson's disease

The primary pathology of PD is a progressive cell loss of selected but heterogeneous groups of neurons. Notably, this process occurs in the melanin-laden dopaminergic neurons of the pars compacta (substantia nigra), selected nuclei in the brain stem, the hypothalamus, cingulate gyrus, olfactory bulb, and sympathetic ganglia and parasympathetic neurons in the intestines.[21] It is believed that the dopamine-deficient state of the substantia nigra results in an increased activity of the internal segment of the globus pallidus and subthalamic nucleus.[22,23] This popular model of basal ganglia circuitry explains akinesia well, but not tremor and rigidity. The model predicts that the inactivation of thalamic nuclei would worsen tremor and that pallidotomy of the globus pallidus interna would produce hemiballism. Thalamotomy has been acknowledged as an effective treatment for PD, as well as essential and other types of tremor,[24] whereas pallidotomy of the globus pallidus interna specifically alleviates levodopa-induced dyskinesia.[25] A surgical lesioning of the globus pallidus interna does not cause hemiballism; however, subthalmic nucleus inactivation commonly does.

Surgical management of Parkinson's disease

There has been a resurgence in functional stereotactic neurosurgery during the 1990s, which reflects the fact that after 5 to 10 years of effective medical therapy with levodopa, patients with advanced PD are accumulating. Furthermore, a greater understanding of the pathophysiology of PD has led to the availability of effective and low-risk surgical procedures. Given that the primary problem in PD is striatal dopamine deficiency, a logical restorative therapy would involve transplantation of dopaminergic cells into the basal ganglia, thus encouraging regeneration of striatal dopaminergic innervation. Transplantation of autologous adrenal medulla to the caudate nucleus has been shown to lack efficacy, however, and it is associated with high mortality and morbidity rates.[26] The transplantation of foetal mesencephalon has shown more promising results,[27-31] although a recent randomised controlled study[32] (2n=40) that used a sham control did not show a clear benefit.[33] Other experimental strategies that have been described recently include porcine xenograft transplantation,[32] intraventricular delivery of dopaminergic neurotrophic factor,[34] implantation of foreign cells in semipermeable polymeric capsules (obviating the need for immunosuppression),[35] and enhancement of tyrosine hydroxylase expression to increase endogenous synthesis of dopamine.[36]

The most common functional stereotactic neurosurgical procedures that are currently performed worldwide for PD are surgical lesioning and deep-brain

Table 1. Comparison of surgical lesioning and deep-brain stimulation

Deep-brain stimulation	Lesioning
Reversible	Nil
Adaptable	Nil
Bilateral procedures possible	Significant morbidity with bilateral procedures
Effective	Effective
High cost	Low cost
Requires regular maintenance including renewal of battery	Single procedure

stimulation of the three overactive nuclei. This region includes the thalamus (nucleus ventralis intermedius or 'Vim') for contralateral tremor; the globus pallidus interna for contralateral rigidity, akinesia and specifically levodopa-induced dyskinesia; and the subthalamic nucleus for all three cardinal symptoms.

Magnetic resonance imaging (MRI) stereotaxy is preferred by the majority of surgeons because of its superior resolution and ease, although spatial distortion can be a problem. Systematic comparison of MRI, computed tomography, and conventional stereotaxy has demonstrated acceptable accuracy.[37] Patients selected should be alert and cooperative, not taking antiparkinsonian drugs, and preferably have florid signs of tremor, akinesia, and rigidity. Confirmation of the surgical target by macrostimulation and assessment of the alleviation of symptoms are key to the success of the procedure.

Whether microelectrode recording (MER) will increase the functional accuracy of target selection is controversial.[38] There is evidence to suggest that MER may increase the risk of the procedure (such as intracerebral haemorrhage) without enhancing accuracy. Generally, if there is concordance between macrostimulation and MER findings, a good result is guaranteed.[39] The risks of intracerebral haemorrhage with this approach is small: 3.3% for each target.[40]

Selecting the target

Thalamic nucleus ablation or stimulation results in consistent contralateral tremor control, but other symptoms of PD will not be affected. Pallidotomy (of the globus pallidus interna) has been shown to relieve contralateral akinesia and rigidity by one third, and levodopa-induced dyskinesia by 92%.[41] The subthalamic nucleus is a small target; suppression of its overactivity leads to alleviation of all three cardinal symptoms of PD.[42] The complication of contralateral hemiballism in subthalamotomy, however, can be significant and has been reported to be as high as one in five.[43] Nevertheless, good results from creating lesions in the bilateral subthalamic nucleus have been reported in the UK[44] and the view that subthalamotomy causes hemiballism has been called into questioned recently by Guridi and Obeso.[45]

Lesioning or deep-brain stimulation?

Although the risk of major complications such as intracerebral haemorrhage and death occurring from unilateral pallidotomy (lesioning by thermocoagulation) is low (4% to 10%), the incidence of permanent adverse effects is reported to be 4% to 46%.[46] Left-sided pallidotomy is associated with reduced verbal fluency,[47] whereas bilateral procedures are associated with dysarthria, dysphonia, and gait disturbance. Deep-brain stimulation has thus become the treatment of choice (Table 1), particularly when left-sided or bilateral targeting is required, because it is not an irreversible procedure. Although there is inadequate data to suggest that deep-brain stimulation of the subthalamic nucleus is superior, the initial experience reported by Limousin[48] favours this strategy.

Gamma-knife radiosurgery

The use of gamma-knife radiosurgery to create a lesion relies on an image without guidance from electrophysiological recordings or macrostimulation assessment. The outcome cannot be determined initially; the median time to clinical response is 2 months, with only half the patients achieving good results.[49,50] A dose-response relationship has also been noted, as has the balance between response and morbidity.[49] Gamma-knife radiosurgery is an option, however, for the patient who is not suitable to undergo standard functional stereotactic procedures.

Local experience

Stereotactic thermocoagulation thalamotomy has been reported in seven cases in Hong Kong.[51] The rarity of the procedure reflects the effectiveness of levodopa in the 1980s. In 1997, deep-brain stimulation—specifically of the nucleus ventralis intermedius—was trialled in two patients with tremor-dominant PD at the Prince of Wales Hospital. The tremor was controlled with improvement in the tremor score in two patients (Table 2). Since 1998, nine rigid-akinetic

Table 2. Tremor score in two patients receiving deep-brain stimulation of the nucleus ventralis intermedius

	Patient 1				Patient 2			
	Pre-DBS*		During DBS		Pre-DBS		During DBS	
Drug treatment	On	Off	On	Off	On	Off	On	Off
Tremor score†	5	6	1	1	3	7	1	1

* DBS deep-brain stimulation
† Score represents the limb contralateral to stimulation; the lower the score, the lesser the severity

Table 3. Bradykinesia score and rigidity score in patients receiving subthalamic nucleus deep-brain stimulation, 1998 to 2000

	Patient 1				Patient 2				Patient 3			
	Pre-DBS*		DBS		Pre-DBS		DBS		Pre-DBS		DBS	
Drug treatment	On	Off	On	Off	On	Off	On	Off	On	Off	On	Off
Rigidity†	0	8	0	2	0	7	0	2	0	8	0	4
Bradykinesia†	5	15	1	9	4	11	4	8	4	14	4	8

* DBS deep-brain stimulation
† Score (United Parkinson's Disease Rating Scale) represents the limb contralateral to stimulation; the lower the score, the lesser the severity

Table 4. Levodopa dosage before and 2 months after deep-brain stimulation procedure

		Levodopa dosage (mg/day)		
Patient No.	Region of brain stimulated	Pre-DBS*	Post-DBS	Reduction in dosage
1	Nucleus ventralis intermedius	300	200	33%
2	Nucleus ventralis intermedius	300	200	33%
3	Subthalamic nucleus	600	500	16%
4	Subthalamic nucleus	2400	1600	33%
5	Subthalamic nucleus	1500	600	60%

* DBS deep-brain stimulation

Table 5. Potential drug cost savings with deep-brain stimulation per patient

Pre-DBS* drug treatment	Dose	Cost (US$ per day)	Post-DBS drug treatment	Dose	Cost (US$ per day)
Levodopa	1500 mg	22.00	Levodopa	600 mg	9.20
Comtan	1000 mg	35.40			
Total cost per day		57.40			9.20
Cost per year		20 951.00			3358.00
Cost saved		US$17 593.00 per year			

* DBS deep-brain stimulation

patients have received deep-brain stimulation of the subthalamic nucleus: seven unilaterally and two bilaterally. Preoperative and 6-month postoperative United Parkinson's Disease Rating Scale scores were recorded for three patients (Table 3). There was no mortality or morbidity noted for the nine patients. One targeting failure occurred in the second patient, who required a subsequent operation approximately 7 months later. In another patient, the extension electrode broke in the neck region after 3 months of satisfactory results; the quadri-electrode was thus replaced.

Microelectrode recording has been performed in the two most recent procedures involving the subthalamic nucleus. A higher degree of confidence in the accuracy of targeting was experienced, at the expense of 2 hours of operating time. There was a significant reduction in levodopa dosage after the stimulation (16% to 60%; Table 4), which is consistent with the results reported in the literature.[48] The cost difference with the reduction of levodopa and the discontinuation of second-line drug treatment can result in an annual saving of approximately US$ 2000 (Table 5).

Conclusion

Although bilateral deep-brain stimulation of the subthalamic nucleus has been described as the treatment of choice,[48] there is so far no randomised controlled trial that confirms its superiority over other treatments. Considering factors such as clinical efficacy and morbidity, as well as the costs associated with a pulse generator, the use of deep-brain stimulation may be favoured for left-sided procedures and lesioning of the right side.[52,53]

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