Malaysian Experience in Deep Brain Stimulation for Parkinson's Disease - Long Term Results

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Summary

A comprehensive functional neurosurgery programme was developed at Sunway Medical Centre (SunMed) for deep brain stimulation (DBS) in 2003. This report documents the outcomes for Parkinson's disease (PD). Criteria for surgery were functional impairment which could not be managed with best medical therapy, and levodopa-induced dyskinesia. We employed MRI-based stereotactic target localisation, augmented with navigation software and microelectrode recording. Between February 2003 and October 2010, 42 leads were implanted in 20 patients. All had bilateral subthalamic nucleus (STN) targetting. 16 patients (80%) showed good improvement in motor function (about 70% reduction in mean UPDRS *on* Motor Score). All except one had significant reduction in dyskinesia scores. Outcomes were poorer in patients who had prior functional surgery. Dosage of medication was reduced by half. At follow-up (1.4 - 92.3 months), functional outcomes were maintained after allowing for age-related decline and disease progression. Our DBS programme for PD has shown sustained benefit in patients for up to seven years.

Introduction

At least 15% of patients with Parkinson's disease become medically refractory and need to consider functional surgery. Deep brain stimulation (DBS) provides more comprehensive benefits, with fewer adverse effects, compared with lesioning surgery. A number of randomised studies have demonstrated the efficacy of DBS[1,2] and the benefits are sustained over periods of five years and beyond.[3,4,5] The SunMed DBS Programme was launched in February 2003 to provide this treatment for Malaysians. This report documents the immediate and long term postoperative outcome in patients with advanced Parkinson's Disease (PD).

Materials and Methods

A clinical protocol was designed for selection and preoperative assessment of patients (Table 1). Criteria for surgery were functional impairment which could not be managed with best medical therapy and levodopa-induced dyskinesia. Indications and exclusions were in accordance with the recommendations of the American Society for Stereotactic and Functional Neurosurgery, the American Association of the Neurological Surgeons, and the Congress of Neurological Surgeons for Deep Brain Stimulation for Parkinson's Disease.[6] SunMed is a private medical centre where all patients are self-funded.

Table 1: SunMed DBS Functional Neurosurgery Programme	
Pre-Operative	Compliance with Selection Criteria[1] Pre-operative Assessment Counselling of patients by Neurologist and Neurosurgeon
Intra-Operative	Target localisation based on MRI and image guidance software Micro Electrode Recording (MER) Macro Stimulation
Post-operative	Programming of stimulator

MRI-based stereotactic target localisation was employed using the Leksell Stereotactic System®, supported with Medtronic StealthStation® navigation software. All patients had electrophysiological mapping with microelectrode recording on the Medtronic Leadpoint® system. Final confirmation of target localisation was performed with MacroStimulation. Medtronic quadripolar leads (Model 3389) were used. Lead fixation was secured using initially the cranial mini-plate, and in subsequent cases, the Navigus cap.

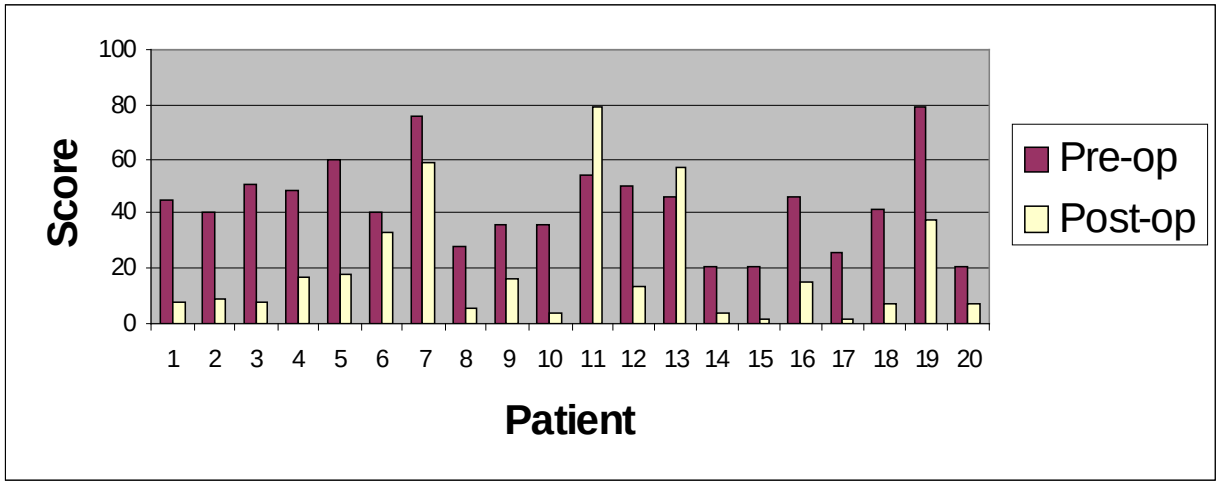
Results

Between February 2003 and October 2010, 42 leads were implanted in 20 patients. Male:female ratio was 1.5:1. Age at surgery was 42 to 71 years with mean of 56.6 years (male 53.5 vs female 61.0). Duration of PD ranged from four years in a young working male to 25 years in the oldest patient, a female aged 71, with mean of 10.6 years. The majority of patients (13 out of 20: 8 male and 5 female) were below 60 years of age. Four patients had previous functional surgery done elsewhere: unilateral pallidotomy (two), bilateral pallidotomy (one), bilateral DBS (one). All patients had electrodes implanted bilaterally in the subthalamic nucleus (STN), except for the sole patient who required unilateral re-do surgery for suboptimal lead placement. Follow up ranged from 1.4 to 92.3 months (mean 60.3 months).

Motor Response

Clinical evaluation was performed using the Unified Parkinson's Disease Rating Scale (UPDRS), with assessment of the Motor Subscale III carried out during medication *on* state. Since these were self-funded patients, cost constraints precluded admission to hospital for *off* period assessments. Optimisation of stimulation parameters was achieved within six months post-surgery. Pre- and postoperative motor scores are shown in Fig. 1.

Fig. 1: Changes in UPDRS Part III Motor *on* scores in 20 patients



Mean motor scores were reduced by 55.2% from baseline of 43.3 to 19.4 postoperative for all patients (Table 2). 16 of 20 patients (80%) were classified as "good responders", defined as at least 50% reduction in UPDRS *on* motor scores. In the good responders, the mean reduction in *on* motor score after surgery was 73.8%.

Table 2: Changes in mean UPDRS Part III *on* Motor Scores: Immediate Postoperative Outcomes

Patient Outcome	Number of patients	Mean UPDRS Part III *on* Motor Score		% Decrease
		Preoperative	Postoperative	
Good Responders*	16	41.7	10.9	73.8
All patients	20	43.3	19.4	55.2

* >50% reduction in UPDRS *on* motor scores

Four patients had unsatisfactory outcome. Causes were prior surgery (two), intracerebral haemorrhage (one) and atypical parkinsonism (one – probable parkinsonism-plus syndrome with initial good levodopa response).

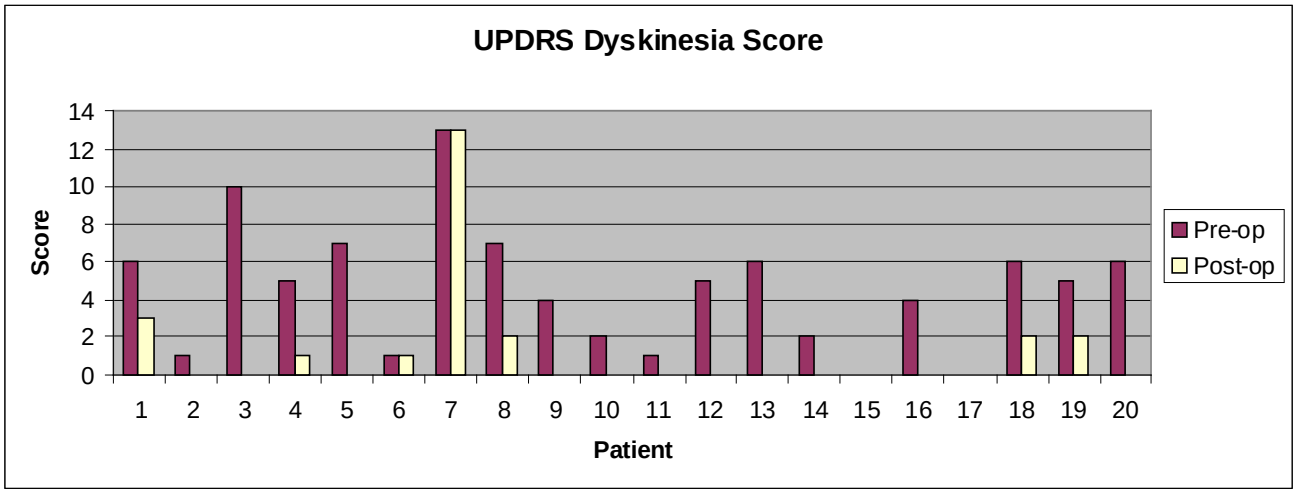
Of the four patients who had prior neurosurgery, only two (50%) had good response; they had previously benefited from unilateral pallidotomy (Table 3). The remaining two patients who had bilateral surgery (DBS and pallidotomy) did not do well.
Dyskinesia was substantially improved, with decrease in *on* dyskinesia scores in all except one patient (Fig. 2). Mean scores were reduced by 52.2% from 4.3 to 2.2.

Table 3: Comparison of Motor Response: Effect of prior functional surgery

Prior functional neurosurgery	Good Responders*	
	No. of Patients	%
No (n=16)	14	87.5
Yes (n=4)	2	50
All patients (n=20)	16	80

* >50% reduction in UPDRS *on* motor scores

Fig. 2: Changes in UPDRS *on* Dyskinesia scores in 20 patients



Medication requirement

Mean daily levodopa equivalent dose was reduced by 47.9% from 869 to 453 mg. In addition to this decrease, our patients were able to reduce or stop supplementary medications for control of pain and sleep disturbance.

Perioperative complications

Two patients had surgical complications: intracerebral haemorrhage in one, and self-limited subdural effusion in the other. The former complication rendered the patient cognitively impaired and wheelchair-bound.

Lead Infection

Two patients developed lead infection which required subsequent ex-plantation and removal of the Implantable Pulse Generator (IPG). One of them opted for repeat implantation with resumption of DBS benefit. The other patient could not raise the necessary funds for repeat surgery.

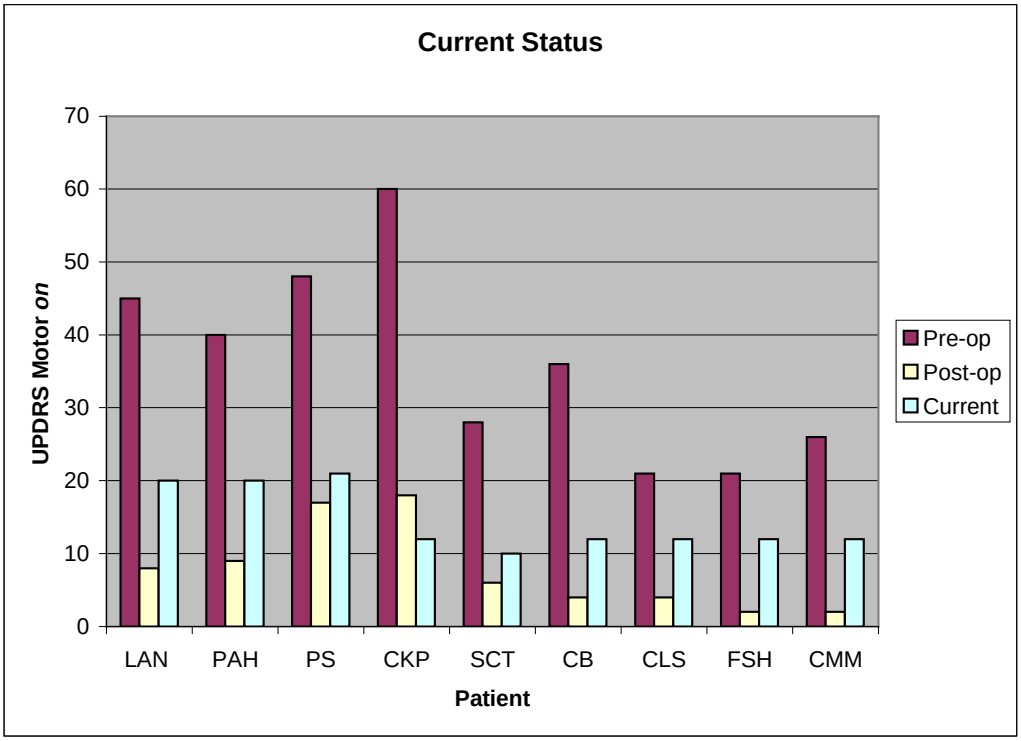
Cognitive changes

Postoperatively, none of the patients developed significant cognitive damage. However, three patients showed subtle personality changes which consisted of mild apathy and loss of drive.

Long term outcome

Over the follow-up period, functional outcomes were maintained in the good responders, all of whom are still ambulant. The older patients (seven are now older than 65) showed mild cognitive and motor deterioration which was consistent with advancing age and disease progression. However, none of them is worse off than before DBS. The oldest patient, now aged 79 years, continues to show benefit after seven years. Of the four poor responders, two have since died from unrelated causes, namely pneumonia and subarachnoid haemorrhage. Up-to-date motor assessments were obtained in nine patients (Fig. 3).

Fig. 3: UPDRS *on* Motor Scores: Current status in nine patients



Replacement of Implantable Pulse Generator (IPG)

To date, eight of the 20 patients have had replacement of the IPG. Two patients had it replaced twice.

Discussion

In their randomised trial of STN DBS, the German Parkinson Study Group (GPS) reported that mean *on* medication UPDRS-III scores at six months were reduced from 18.9 to 9.3 (22.8%).[2] In comparison, our *on* motor scores were reduced by about half overall, and about 70% in the good responders. It is likely that our patients showed more improvement because of greater disease severity, since our preoperative mean motor score was 43.3. We believe these results were achieved by augmenting anatomic targetting with physiological localisation using microelectrode recording.

Decrease in medication requirement has been widely documented after STN DBS. Our patients' reduction in dosage by about half is similar to other studies. Levodopa equivalent dose (LED) reductions range from 37.3% (The Deep-Brain Stimulation For Parkinson's Disease Study Group[1]) to 49.2% (the GPS Study[2]).

Concerning surgical morbidity, we had a case of cerebral haemorrhage (1 out of 20, 5%). As for the cause, we considered transient increase in blood pressure in the immediate post-operative period due to extreme stress. This patient had become emaciated and physically exhausted by prolonged duration of motor fluctuations with severe dyskinesia. In retrospect, a period of nutritional and fitness build-up may have obviated this complication.

Regarding the effect of previous neurosurgery, it was reported that patients with prior pallidotomy derive less improvement from STN DBS.[7] However, our good responders included two patients who had unilateral pallidotomy, whereas poor outcomes followed bilateral surgery (pallidotomy and DBS implantation). Although the numbers are small, these results suggest that bilateral lesioning or multiple passes for electrode placement may adversely affect outcome.

Dyskinesia scores were substantially reduced in our patients, in keeping with the documented benefit of STN DBS.[1,2] This benefit is attributed to lower doses of dopaminergic medications as well as an anti-dyskinetic effect. It has recently been suggested that STN DBS raises the threshold for the appearance of dyskinesia.[8] Nevertheless, it should be noted that this score was also reduced in three of our poor responders, and hence cannot be taken in isolation as an indicator of good response. The reasons for this decrease may be reduced medication intake, as well as abolition of dyskinesia through neuronal loss from cerebral haemorrhage, parkinsonism-plus syndrome and cumulative damage from lesioning and multiple electrode passes.

In our centre, IPG replacement could be viewed as a surrogate indicator of efficacy. Since DBS is a self-pay treatment and a new battery is a significant expense, decision to replace the IPG can be taken as confirmation of genuine benefit. Among the good responders, all had opted for replacement IPG except for two patients who could not raise the necessary funding.

Finally, similar to some DBS studies, our series has an excess of male patients (male:female ratio of 1.5:1 vs 1:1.04 in a Malaysian hospital study[9]). Possible reasons include the need to regain fitness for employment and our self-pay mode of medical treatment. The twelve male patients were younger on average, with eight of them below 60 years of age.

Conclusions

In our experience, DBS is an effective and safe treatment option for medically intractable PD. Our DBS programme has shown sustained benefit for up to seven years in Malaysian patients. Outcomes are better in patients without prior surgery, although good response may be achieved after unilateral pallidotomy. Better patient selection and further refinement of operative techniques will be the key to improved results.

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