DEEP BRAIN STIMULATION (DBS)
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EXECUTIVE SUMMARY

Introduction

Therapeutic Deep Brain Stimulation (DBS) for movement disorders emerged from seminal observations by pioneering functional neurosurgeons in the 1950s and since the 1990s is a surgical procedure used to treat advanced Parkinson’s disease (PD). DBS uses a surgically implanted, battery-operated medical device called a neurostimulator, similar to a heart pacemaker and approximately the size of a stopwatch, to deliver high-frequency electrical stimulation to specific targeted areas in the brain via implanted electrodes. This electrically silences the abnormal activity that causes tremor and PD symptoms producing a virtual lesion.

At present, the cost of DBS surgery in the Malaysian government-funded hospitals is approximately RM85,000 for the first surgery and a further RM65,000 for the periodic replacement of the pulse generator (battery), once every 3 to 5 years.

Objective/Aim

The objective of this technology review was to assess the safety, effectiveness / efficacy and cost-effectiveness of Deep Brain Stimulation (DBS) for treatment of patients with advanced Parkinson’s disease (PD).

Results and Conclusions

There was limited but fair level of evidence (Level II-2) to show that Deep Brain Stimulation (DBS) for treatment of patients with Parkinson’s disease (PD) is safe and effective. United States Food & Drug Administration (USFDA) has approved DBS as a treatment for PD in 2002. However, there was no retrievable evidence on the CE mark for this technology.

There was also very limited evidence to show the cost-effectiveness of DBS for treatment of patients with PD.

Methods

Electronic databases were searched, which included PubMed, Medline, Journal @ Ovid full text via OVID, OVID EBM Reviews - Cochrane central register of controlled trials, EBM Reviews - Cochrane database of systematic review, Horizon scanning databases - Centre, Birmingham, Australia and New Zealand Horizon scanning (ANZHSN), FDA website, MHRA website and from non scientific database - Google search engine. In addition, a cross-referencing of the articles retrieved was also carried out accordingly to the topic. Relevant articles were critically appraised and evidence graded using US / Canadian Preventive Services Task Force.
DEEP BRAIN STIMULATION (DBS)

1.0 INTRODUCTION

Parkinson’s Disease (PD) is a progressive neurodegenerative disease of the brain. Despite best medical therapy that includes levodopa, the motor and non-motor disabilities of patients will continue to deteriorate over time. After a ‘honeymoon’ period of five to seven years’ treatment, dyskinesias (involuntary body movements that may emerge as a side effect of PD medications) become more frequent, and add to the sufferings of most Parkinson patients. As such, in the advanced stage of PD (eight to 15 years after the onset of illness), the quality of life (QoL) is significantly impaired.  

DBS is a surgical procedure used to treat a variety of disabling neurological symptoms. Since the late 1990s, DBS has been used as a treatment in PD and is indicated when, despite a good response to levodopa, patients are disabled by dyskinesias, ‘off’ symptoms, tremor, or any combination of these three. It is the appropriate selection of patients, the matching of patients to the specific DBS procedure appropriate for his / her symptom profile and the experienced and careful intraoperative surgical routine that determine how successful DBS will be. DBS will never make someone better than their best response to levodopa. i.e DBS will not improve symptoms that do not respond to levodopa. Tremor is the exception, which more than any other symptom, reponds well to DBS.  

Different sites in the basal ganglia region are established and approved targets for such stimulation. Since 1993, high-frequency bilateral subthalamic (STN) stimulation has been the standard neurosurgical procedure for the treatment of advanced idiopathic PD. The posteroverntal globus pallidus interna (GPi) is the target of choice for DBS in the treatment of levodopa-induced dyskinesias and dystonia while emerging data suggests low frequency stimulation of the pedunculopontine nucleus (PPN) may improve levodopa-resistant axial symptoms. However, dementia and cognitive deficits are not improved by DBS while atypical Parkinsonisms are usually not significantly improved by STN stimulation.  

Post-operatively, DBS stimulator programming can be time-consuming, particularly in the first few months after surgery and adequate time should be allowed for adjustment sessions. Selection of electrical parameters is usually guided by therapeutic impact on symptoms and avoidance of side effects. ‘Trouble shooting’ of the integrity of the circuit, battery status and any hardware failure alongside periodic review of changing parameters will usually be carried out during follow-up assessments.  

At present, the cost of DBS surgery in the Malaysian government-funded hospitals is approximately RM85,000 for the first surgery and a further RM65,000 for the periodic replacement of the pulse generator (battery), once every 3 to 5 years.  

This technology review was conducted following a request from the Director of Medical Development Division, Ministry of Health Malaysia who received a letter from the Lloyd Tan Parkinson’s Trust Fund, asking for the feasibility and cost-effectiveness of this procedure in Malaysia.
2.0 OBJECTIVE/AIM

The objective of this technology review was to assess the safety, effectiveness / efficacy and cost-effectiveness of Deep Brain Stimulation (DBS) for treatment of patients with advanced Parkinson’s disease (PD).

3.0 TECHNICAL FEATURES

Figure 1: Deep Brain Stimulation System
Figure 2: Deep Brain Stimulation (DBS)

DBS uses a surgically implanted, battery-operated medical device called a neurostimulator, similar to a heart pacemaker and approximately the size of a stopwatch, to deliver high-frequency electrical stimulation to specific targeted areas in the brain via implanted electrodes. This electrically silences the abnormal activity that causes tremor and PD symptoms producing a virtual lesion.3

The DBS system consists of three components: the lead, the extension, and the neurostimulator. The lead (also called an electrode) is a thin, insulated wire inserted through a small opening in the skull and implanted in the brain. The tip of the electrode is positioned within the targeted brain area. The extension is an insulated wire that is passed under the skin of the head, neck, and shoulder, connecting the lead to the neurostimulator. The neurostimulator (the “battery pack”) is the third component and is usually implanted under the skin near the collarbone. In some cases it may be implanted lower in the chest or under the skin over the abdomen. Once the system is in place, electrical impulses are sent from the neurostimulator up along the extension wire through the lead into the brain.3
4.0 METHODOLOGY

4.1 Searching

Scientific databases such as PubMed, Medline, OVID EBM Reviews - Cochrane central register of controlled trials, EBM Reviews - Cochrane database of systematic review, EBM Reviews - HTA databases, Horizon scanning databases - Centre, Birmingham, Australia and New Zealand Horizon scanning (ANZHSN), FDA website, MHRA website and from non scientific database - Google search engine were searched for evidence of safety, effectiveness/efficacy and cost-effectiveness of Deep Brain Stimulation (DBS) for treatment of patients with Parkinson’s disease (PD).

The following keywords were used either singly or in combinations: Deep brain stimulation, safety, adverse events, effectiveness, cost-effectiveness, Parkinson’s disease.

4.2 Selection

All published articles related to safety, effectiveness / efficacy and cost-effectiveness of Deep Brain Stimulation (DBS) were included. Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP) and evidence was graded according to US/Canadian Preventive Services Task Force (Appendix 1).

5.0 RESULTS AND DISCUSSION

The search strategies yielded an article on the United States Food & Drug Administration (USFDA) related to Deep Brain Stimulation (DBS). There were three articles related to the safety and effectiveness / efficacy of DBS. However, there was only one retrievable evidence on the cost-effectiveness of this technology.

5.1 Safety

USFDA has approved DBS as a treatment for PD in 2002. However, there was no retrievable evidence on the CE mark for this technology.

Helene GB et al. 2009 conducted a cohort study to determine the long-term efficacy and safety of bilateral subthalamic nucleus (STN) stimulation in advanced Parkinson’s disease (PD). The study showed that among the 42 initial patients, they observed the following: two brain haemorrhages, three infections of the device, two phlebitis and one pulmonary embolism. In addition, two patients needed a repositioning of the electrode. Among the 23 patients followed at 5 years, long lasting side effects consisted of dysarthria (56%), depression (39%), eyelid opening apraxia (30.4%) and apathy (4.3%). The authors concluded that the side effects related to the surgical procedure, the device, and the stimulation were mild and rare. Level II-2

Another study was conducted in 2007 by Tir M et al. to prospectively assess the impact of subthalamic nucleus (STN) deep brain stimulation (DBS) at 12 months after surgery in a 103 consecutive patients with severe Parkinson’s disease (PD). The main surgical complications after STN-DBS were as follows: infections (n=7), intracerebral hematomas (n=5), electrode fractures (n=4), and incorrect lead placements (n=8). They also observed
cognitive decline and depression in 7.7% and 18% of the patients, respectively. The authors concluded that in contrast to efficacy, the occurrence of adverse events cannot be predicted.6

Tabbal S et al. 2007 conducted a cohort study to establish the safety and efficacy of bilateral subthalamic nucleus (STN) deep brain stimulation (DBS) in Parkinson’s disease (PD) patients with disabling motor fluctuations performed with an expedient procedure with limited intraoperative mapping. Surgical complications were assessed from all 110 patients who underwent operation during the study period. Adverse effects associated with STN-DBS were as follows: Surgical adverse effects: intraventricular haemorrhage, mild transient facial palsy and ptosis, several hours of postoperative agitation and confusion, intraoperative confusion that did not allow placement of the contralateral stimulator, psychosis and depression, progressive dementia, severe dyskinesia, and cardiac arrhythmia; DBS-induced adverse effects: affective changes due to excessively deep placement of one electrode, severe dyskinesia and DBS-induced blepharospasm; and in hardware-related problems: lead replacement due to short-circuit, revision of the lead connector, replacement of the DBS system on one side as a result of infection, bilateral pulse generator infections requiring removal of both DBS systems, and pulse generator revision due to skin erosion. The study indicated that adverse effects were infrequent and transient with no incident of death, hemiparesis, or seizure.7

5.2. Effectiveness / efficacy

From the study conducted by Helene GB et al. 2009, 42 consecutive patients with idiopathic PD underwent a surgical procedure for bilateral STN stimulation. Clinical evaluation was performed one week before surgery, and again at one and five years postoperatively with the Unified Parkinson’s Disease Rating Scale (UPDRS), Mattis Dementia Rating Scale and the Beck Depression Inventory (BDI). These assessments were performed before surgery under two conditions. First, after intake of a supraliminar dose of levodopa (on medication) and secondly, after antiparkinsonian medication withdrawal of at least 12 hours (off medication). Postoperative evaluation was conducted under four conditions: on-stimulation and off-medicine; off-stimulation and off-medicine; on-medicine and off-stimulation; and on-medicine and on-stimulation. They found that STN stimulation reduced the UPDRS motor score by 55% compared to baseline in the off-medicine conditions at 5 years. Tremor, rigidity, bradykinesia, postural stability, and gait improved by 74%, 66%, 59%, 17% and 37%, respectively. UPDRS part II scores (Activities of Daily Living / ADL) were reduced by 38%. The dopaminergic treatment daily dose was reduced by 54.4% after surgery. The authors concluded that bilateral STN stimulation remains the best alternative to medical treatment for advanced PD.5

Tir M et al. 2007 conducted a study on the impact of STN-DBS at 12 months after surgery in a 103 consecutive patients with severe PD. They received bilateral STN-DBS in Lille University Medical Centre, Lille, France between May 1998 and March 2003. Clinical assessment was performed before and 12 months after surgery and was based on the Unified Parkinson’s Disease Rating Scale (UPDRS) Parts II, III, and IV A; the Schwab and England (S&E) scale; and cognitive evaluation. Patient-rated overall improvement was also evaluated. The study revealed that under the off drug/on stimulation condition, the UPDRS Part III score (motor symptoms) at 1 year had
decreased by 43%. In the off drug/on stimulation condition, the UPDRS Part II scores (ADL) fell by 34%. The score on the S&E scale improved by 45% compared with the pre-surgery off drug condition. Moreover, in the on drug/off stimulation condition, the UPDRS Part IV A score (severity of dyskinesia-related disability) decreased by 61%. The mean patient-rated overall improvement score was 70.7%. The authors concluded that the efficacy of STN-DBS in their centre is generally comparable to that achieved by other group, albeit near the lower limit of the range of reported values.

From the same cohort study conducted by Tabbal S et al. 2007, the efficacy of the procedure was assessed in the 72 patients who underwent follow-up evaluations from 3 to 12 months post-operatively. All evaluations included ratings on the motor section of the Unified Parkinson’s Disease Rating Scale (UPDRS) with stimulation off for at least 30 minutes and then repeated after stimulation was on for at least 10 to 15 minutes. It was demonstrated that in the 72 patients, STN DBS reduced total UPDRS motor scores at the time of the follow-up evaluation by 47% from 43.4 ± 16.1 with stimulators off to 22.8 ± 11.6 with stimulators on (P < 0.001). The changes in UPDRS motor subscores improved as follows: rest tremor, 74% (P < 0.001); rigidity, 58% (P < 0.001); bradykinesia, 37% (P < 0.001); pull test, 35% (P < 0.001); gait, 44% (P < 0.001); axial signs, 42% (P < 0.001); and speech, 13% (P < 0.001). The authors concluded that the STN DBS surgical technique for PD is expedient with effective outcomes and low complication rates.

5.3. Cost-Effectiveness

Tomaszewski K and Holloway R conducted a cost-effectiveness analysis. This analysis utilizes semi-Markov processes within a transitional probability decision model to estimate the incremental cost-effectiveness of Deep Brain Stimulation (DBS) compared with best medical management (pharmacotherapy). Analysis is limited to those Parkinson’s disease (PD) patients aged 50 years or older who are in the later stages of the disease with intractable motor fluctuations. As the long-term efficacy of DBS (> 3 years) is not known, key assumptions regarding the procedure’s long-term durability were made. Costs were in US dollars (USD) - 2000 and quality-adjusted life years (QALY) was the effectiveness measure. Base assumptions were that quality of life (QoL) in patients with late-stage PD is 0.55 (0-to-1 scale, 1 is perfect health) and that DBS benefits are constant for 4 years, eroding gradually over the next 5 years until at parity with those produced by best medical management. Incremental cost-effectiveness and sensitivity analyses were performed. For incremental cost-effectiveness ratio (ICER) up to $35,000, the authors consider such ranges cost-effective. For ICER greater than $100,000, they consider such ranges as probably not cost-effective. For that ICER between $35,000 and $100,000, the cost-effectiveness remains uncertain. From this analysis, they indicated that under base-case assumptions, DBS provides an additional 0.72 QALY at an additional cost of $35,000 compared with best medical management. This is equivalent to an ICER of $49,000. The authors concluded that DBS can be cost-effective and should be further tested and refined through randomized, controlled, prospective experiments including QoL and economic components.

The World Health Organization’s (WHO) Commission on Macroeconomics and Health recommends that an intervention be considered as cost-effective if the cost per QALY is less than three times the per capita Gross Domestic Product (GDP). GDP per capita
(Malaysia)\textsuperscript{10} in year 2000 was USD $4,029.90 and the ICER from the selected article was USD $49,000. This suggests DBS is not cost-effective in Malaysia based on the above WHO guideline.

6.0 CONCLUSION

6.1. Safety

There was limited but fair level of evidence (Level II-2) to show that Deep Brain Stimulation (DBS) for treatment of patients with advanced Parkinson’s disease (PD) is safe. USFDA has approved DBS as a treatment for PD in 2002. However, there was no retrievable evidence on the CE mark for this technology.

6.2. Effectiveness / efficacy

There was limited but fair level of evidence (Level II-2) to suggest the effectiveness / efficacy of Deep Brain Stimulation (DBS) for treatment of patients with advanced Parkinson’s disease (PD).

6.3. Cost-Effectiveness

There was very limited evidence to show the cost-effectiveness of Deep Brain Stimulation (DBS) for treatment of patients with Parkinson’s disease (PD).

7.0 REFERENCES

1. Malaysian Parkinson’s Disease Information Centre: Lloyd Tan Parkinson’s Trust Fund. Available at http://www.lloydtan-trust.com


10. Malaysia in Figure. Available at http://www.nationsonline.org/oneworld/Country-Stats/Malaysia-statistics.htm

8.0 Appendix

8.1 Appendix 1

Designation of Levels of Evidence

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

Source: US/Canadian Preventive Services Task Force (Harris 2001)