

Anaesthesia and deep brain stimulation

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Abstract

Deep brain stimulation (DBS) is becoming an increasingly popular minimally invasive surgical procedure for various movement disorders, especially Parkinson's disease. Different nuclei have been identified depending on patients' symptoms, but the success or failure of the procedure depends on various other factors such as proper patient selection and risk-benefit analysis. While various techniques of anaesthesia including monitored anaesthesia care, conscious sedation and general anaesthesia are being used routinely, no clear-cut evidence exists as to the best technique for this procedure. This review article discusses the surgical procedure of DBS, devices currently available, perioperative anaesthetic concerns and techniques, effect of anaesthetic drugs on microelectrode recordings and macro-stimulation and associated complications.

Key words: Anaesthesia, deep brain stimulation, Parkinson's disease

INTRODUCTION

Parkinson's disease (PD) is a chronic, progressive, neurodegenerative disease characterised by four cardinal motor features (postural instability, rigidity, bradykinesia and resting tremors) and some non-motor features such as anxiety, depression, impaired cognition and autonomic dysfunction. PD occurs due to an imbalance between dopaminergic and cholinergic neurons in the brain. Initially managed with medical treatment, PD patients are considered for deep brain stimulation (DBS) when medical therapy seems inadequate. Functional stereotactic neurosurgery has expanded in the recent past to include several diseases, and DBS has become an increasingly common procedure for PD over the past

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few years. DBS is a minimally invasive procedure used for the treatment of neurological disorders such as PD, movement disorders and certain psychiatric conditions.

HISTORY

Early surgical procedures for PD involved making lesions in deep brain structures such as thalamotomy, pallidotomy and cingulotomy. The role of basal ganglia in body movements was appreciated in early part of the 20th century, and the development of stereotactic frames in the 1940s and 1950s led to surgeries being performed on basal ganglia, which were considered surgical no-go areas until then.^[1] Thalamic surgery was found to relieve tremors and using microelectrode recordings (MERs), the ventralis intermedius (Vim) subdivision of thalamus was identified as the target nucleus for tremors. However, these lesioning surgeries were irreversible and were associated with permanent side effects such as paresis, confusion, dysarthria and gait disturbances.^[2] With the advent of Levodopa in 1968, these surgical procedures has largely been stopped. However, as complications of long-term levodopa use, especially motor fluctuations, were

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identified and with development of high-resolution computed tomography (CT) and magnetic resonance imaging (MRI) techniques to identify target areas for DBS, these surgeries came back into practice in the early 1990s. Initially, the target of interest was thalamic nuclei which gradually shifted to the globus pallidus interni (GPi) and subthalamic nucleus (STN), when they were identified as being overactive in PD.

In 1975, the concept of stimulation rather than ablation of deep brain structures for treatment of movement disorders emerged. DBS was first developed in 1987 by Professor and Neurosurgeon Dr. Alim-Louis Benabid in France. Being reversible along with the option of placing bilateral electrodes and the ability to modulate stimulation, DBS has become an increasingly famous surgical option for PD. DBS was approved by the Food and Drug Administration (FDA) in 1997 in the United States and has been found to be safe with long-term benefits.^[3] While being beneficial, DBS surgery can be associated with several complications, is more expensive and time-consuming and needs specialised personnel and periodic battery replacement.

After being used for PD initially, DBS uses have now been expanded to various other movement disorders, psychiatric illnesses, chronic pain, epilepsy, etc.

INDICATIONS

- PD: DBS neither offers cure for PD nor does it change disease progression. Tremors, rigidity and bradykinesia are the motor symptoms that improve with DBS. Non-motor symptoms such as mood, energy level and general sense of well-being also improve with DBS. Patients with pre-operative levodopa responsiveness,^[4] duration of disease >5 years, age <70 years respond well to DBS
- Tremors: Dystonia patients with severe disabling tremors affecting daily activities can be considered for DBS. Intention or resting tremors of distal extremities are more responsive than those more proximal^[5]
- Dystonia: Dystonia which is refractory to all drugs including botulinum toxin has shown good response to DBS surgery. Primary generalised dystonia, idiopathic cervical dystonia and juvenile-onset dystonia have shown good response^[6]
- Psychiatric illnesses: Surgery can be considered in these patients when other therapies have failed. Results of DBS in patients with obsessive-compulsive disorder appear promising^[1]
- Alzheimer's disease, Huntington's chorea
- Chronic pain.

CONTRAINDICATIONS

DBS should not be considered for patients with adequate control of symptoms with medications. Patients with a diagnosis of PD for <5 years duration and age >70 years are considered relative contraindications for DBS. Furthermore, DBS does not help reduce dopamine unresponsive symptoms such as walking, talking and thinking problems. Patients with psychiatric illnesses, cognitive derangements such as dementia also should not be considered for DBS since STN-DBS has been shown to be associated with higher incidence of depression and cognitive deficits post-operatively.^[7]

Patients with increased bleeding risk (coagulopathy, uncontrolled hypertension), severe coronary artery disease, diabetes mellitus, active cancer or infection, patients requiring short wave, microwave or therapeutic ultrasound diathermy, patients who will be exposed to MRI using a full-body radio-frequency coil and patients who cannot operate stimulator properly also should not be considered for DBS.^[8] The presence of pacemaker is not a contraindication although extra precautions need to be taken.

MECHANISM OF ACTION

It was recognised in the late 1970s and 1980s that high-frequency electrical stimulation of deep brain structures has the same effect as lesioning of these structures. How DBS works is exactly not known. It is thought that electrical stimulation of deep brain structures inhibits cell firing and excites axons, leading to the release of calcium which causes release of neurotransmitters which reduce symptoms of PD.

The effect of DBS varies with the site of stimulation. The target sites depend on patients' symptoms and include the STN, GPi or Vim. The stimulators are set at a high frequency of around 130–180 Hz to suppress overactivity in the target nuclei. The Vim nucleus is preferred for patients with tremors as predominant symptoms, but it does not provide relief of rigidity, bradykinesia, dyskinesia, etc. The STN/GPi is used for patients with symptoms other than tremors as predominant symptom. STN has been found to be superior to GPi with respect to improvement in motor scores^[9] and has even been used for patients with GPi-DBS failure. The effects of DBS are frequency dependent with maximum relief at >100 Hz and no relief at <50 Hz.

SURGICAL PROCEDURE

DBS surgery is performed in two stages: (1) Placement of electrodes in target nuclei and (2) internalisation of leads and subcutaneous placement of implantable

pulse generator (IPG). The electrodes can be placed unilaterally or bilaterally depending on patients symptoms. DBS on one side of the brain helps improve symptoms on opposite side of the body. The entire procedure can be completed in one sitting or as a two-staged procedure, where internalisation of electrodes and placement of pulse generator is done 3 days to 2 weeks later, depending on the duration of procedure and patient cooperation. Another reason for performing a two-staged procedure is the 'microlesion effect' which occurs due to oedema around the freshly implanted electrodes causing improvement in symptoms without any stimulation and can impair the ability to test the beneficial effects of stimulation.^[10]

Placement of electrodes is a stereotactic procedure. The specific targets for electrode insertion are identified using frame-based imaging. STN and GPi are visible on stereotactic MRI, whereas thalamic nuclei are not.^[8] The surgical procedure starts with the placement of a rigid head frame to the patients' head, and MRI (CT scan, if MRI is not feasible) is carried out to visualise brain structures. Commonly used head frames are Leksell frame and Cosman–Roberts–Wells frame. However, the presence of these frames makes access to airway difficult. After surgical planning based on scans, the patient is shifted to operation theatre where supine or semi-sitting position is commonly used with the head frame fixed to the operating table. A burr hole is made for electrode insertion. The electrode is inserted by the neurosurgeon 10–15 mm above the target site and then advanced in 0.5–1.0 mm increments while the neurophysiologist identifies the target nuclei using MERs. These recordings are obtained as the microelectrode is passed towards the target nucleus and neuronal activities are simultaneously recorded.^[8] Specific brain regions have unique patterns of spontaneous neuronal firing which help in the identification of exact target nuclei. The variations in spontaneous firing rates among different nuclei and variations with movement help identify the specific target. MER may take several hours. Once appropriate area is identified, macro-stimulation testing is performed to look for improvement in patients' symptoms and any side effect. Once the location of electrode is confirmed radiologically, it is secured and the wound is closed. The electrodes are then connected to extension cables which are tunnelled subcutaneously through the side of neck and connected to the IPG placed subcutaneously below the clavicle or in the abdominal wall. If performed as a two-staged procedure, the electrodes are temporarily connected to an external pulse generator. DBS programming is generally done 4 weeks after the placement of electrodes to avoid microlesion effect and may take several sittings to achieve adequate control of symptoms.

DEEP BRAIN STIMULATION DEVICES

At present, a device manufactured by Medtronic under the brand name Acliva® Parkinson Control Therapy has FDA approval for clinical use.

The DBS system consists of lead, just over a millimetre in diameter, which has four electrode contacts at its tip. An anchoring system (plastic ring) fixes the electrode to the skull. The electrode is connected by a wire to the pulse generator. Currently, three types of pulse generators are available: Some for unilateral stimulation of electrodes (single chamber), some for bilateral (dual chamber) and some rechargeable. The pulse generator is adjusted using a programmer which communicates with the pulse generator using radio waves when held over it and regulates the electricity delivered to the electrodes. A patient controller is also available which allows the patient to turn the pulse generator on or off, check battery status and make self-adjustments in the IPG parameters. The battery life of these devices is generally 2–5 years and the rechargeable ones can last up to 9 years. It is recommended to replace the battery when its life is 10% or less and is done as an outpatient procedure.

PRE-OPERATIVE EVALUATION

The success of DBS therapy depends on careful patient selection and thorough assessment of risk and benefit for each individual patient. Up to 30% of DBS surgery failures have been attributed to improper patient selection.^[11] A multidisciplinary team consisting of neurosurgeon, neurologist, neuropsychiatrist, neurophysiologist and psychologist must evaluate the patient for suitability for surgery. Factors to be considered include general condition of patient, psychiatric history, cognitive function (especially dementia), level of disability, life expectancy, familial support, risk factors for complications, expectations of patient and response to medical treatment.^[12] Generally, patients with advanced disease, those with good response to medical treatment, medication-induced dyskinesias, medication-refractory tremors, intolerance to medications, younger age and without cognitive or psychiatric illnesses do well with DBS therapy.^[13]

Along with routine pre-operative assessment, pre-anaesthetic check-up must consider other specific challenges in this patient population.

Patient-related factors that must be considered include comorbid medical conditions, age of the patient, history of obstructive sleep apnoea, ability to cooperate during the procedure and presence of ferromagnetic implants (such as aneurysm clips, pacemaker, cochlear implants, internal cardioverter defibrillator). Hypertension should

be adequately controlled to prevent haemorrhage during insertion of electrodes.

Procedure-related considerations include difficult airway access due to the presence of head frame. Thorough airway assessment and equipment for securing airway at any stage of the procedure are essential. Laryngeal mask airway (LMA) and fibre-optic intubation are the most feasible options in case of emergency. Generally, removal of head frame is avoided for intubation, but anaesthesiologist must always be provided with frame opening equipment, in case frame removal is required. Other considerations are that anaesthesia might have to be provided in remote locations such as MRI chamber apart from operation theatre. The presence of all emergency equipment in working condition must be ensured. Intraoperative positioning may be difficult in patients with movement disorders. Patients operated upon in semi-sitting position have higher risk of venous air embolism (VAE), hypovolaemia, etc., In addition, prolonged nature of these surgeries and inability to move can cause patient fatigue. Effect of anaesthetic drugs on MERs must also be considered.

Additional considerations to be remembered depending on specific disease entity are^[14] risk of haemodynamic instability, aspiration and laryngospasm, poor cough, anaemia, depression, hallucinations, dementia and potential drug interactions in patients of PD. Patients with dystonia are at increased risk of haemodynamic instability, laryngospasm, etc. Patients with essential tremors are prone to bradycardia and other arrhythmias. Patients with epilepsy often have developmental delay and are on medications that have interactions with anaesthetic drugs. Chronic pain patients need optimisation of pain medications peri-operatively.

Standard fasting regimen is followed. Pre-operative neurological status must be documented and patient should be explained thoroughly about what to expect during the procedure, long-term outcomes and perioperative medication management. Need for invasive monitoring is decided based on comorbid conditions and intraoperative patient positioning. Pre-medication drugs must be given cautiously. Benzodiazepines, opioids and other sedatives are better avoided since they can interfere with intraoperative interpretation of tremors and patients ability to cooperate. Antihypertensive medication should be continued. Disease-specific drugs are continued or discontinued after discussion with neurosurgical team. Some patients need to be in drug-off state so that intraoperative mapping can be done. However, this can worsen symptoms. In patients with severe symptoms, reduced dose of these drugs may be given in conjunction with neurosurgical teams' advice. Drugs used for control of motor symptoms are generally withheld overnight and on the morning of surgery.

TECHNIQUES OF ANAESTHESIA

The goals of anaesthesia are to provide adequate operating conditions, facilitate neuromonitoring to localise the target, have an alert and cooperative patient with a safe airway and diagnose and treat any complications. Various techniques have been described depending on patients' condition and neurosurgeons requirements. These include monitored anaesthesia care with local anaesthesia, conscious sedation and general anaesthesia. At present, there is no consensus as to the best anaesthetic technique. Most institutions have developed their own techniques based on surgeons' requirements and individual preferences.

The application of stereotactic frame is generally achieved with local anaesthetic infiltration of pin site. A combination of supraorbital and greater occipital nerve blocks may be better.^[15] Some patients may require sedation or general anaesthesia, especially those with dystonia, uncooperative patients, chronic pain and paediatric patients. Use of propofol or dexmedetomidine infusion has been described for sedation. In such cases, anaesthesiologist must have adequate equipment ready, considering the remoteness of location. Airway management, when required, must ideally precede placement of frame. If anaesthesia is required after frame placement, then direct laryngoscopy will be difficult. LMA or fibre-optic intubation may be used, but the risk of regurgitation and aspiration must be considered with LMA use.

After frame placement, patient is shifted to the operation theatre. Intravenous access is established and monitors are applied. Standard monitoring with electrocardiogram, noninvasive blood pressure, SpO₂ and end-tidal CO₂ is done. Invasive blood pressure monitoring may be done in selected cases. Depth of anaesthesia monitoring using bispectral index (BIS) may be done; however, its usefulness in DBS is not well established.^[16] Fluid input and output must be monitored. Urinary catheter may be omitted in an awake patient. Proper positioning of the patient is essential. The neck is kept slightly flexed at lower cervical spine and extended at atlanto occipital junction. Legs are flexed and supported at the knees. Patients with history of obstructive sleep apnoea may need continuous positive airway pressure therapy intraoperatively.

Monitored anaesthesia care

An awake patient offers the benefit of intraoperative brain mapping and macro-stimulation for target localisation and is therefore preferred. In the awake patient, local anaesthetic (commonly bupivacaine, lidocaine, ropivacaine)^[17] is infiltrated at site of burr hole. Scalp block is an alternative and has been shown to be less painful.^[15] However, local anaesthetic toxicity is a concern

with scalp block. Ropivacaine doses of up to 4.5 mg/kg have been found to be safe.^[18] Patient can have a feeling of ring-like tightness that can persist for up to 5 min after application of pins. Patient must be explained and prepared mentally for these occurrences preoperatively. In case of prolonged procedures, additional infiltration for wound closure may be required. Adequate pain control, avoiding excessive fluid administration, careful positioning and temperature management are essential intraoperatively. Supplemental oxygen is administered with nasal prongs or mask. Good communication with the patient must be maintained throughout the surgery.

Conscious sedation

Using short-acting drugs and stopping before testing can provide optimal conditions for MER and stimulation testing. Commonly used drugs are propofol, dexmedetomidine and opioids, especially during opening and closure of procedure. Benzodiazepines are generally avoided since they abolish MER. Propofol infusion at a rate of 50 µg/kg/min^[19] has been widely used and can be combined with fentanyl or remifentanyl infusion. Dexmedetomidine may be a better alternative for MER. It also provides added advantages of analgesia and minimal respiratory depression and does not ameliorate clinical signs of PD.

General anaesthesia

General anaesthesia is generally required for patients with psychiatric or cognitive dysfunction, severe dystonia or off-drug movements, severe fear or anxiety and paediatric patients. Intraoperative mapping and stimulation is not possible with general anaesthesia but can be used with careful titration of anaesthetic drugs and limited mapping. Generally, an asleep-awake-asleep technique is used where the patients are anaesthetised during the initial and later part of surgery and awake during mapping phase. Volatile, intravenous or a combination of both has been used. Volatile anaesthetics are used at a minimum alveolar concentration (MAC) of <1. BIS score of around sixty is targeted. Although anaesthetic drugs can interfere with MERs, use of general anaesthesia has not been shown to worsen improvement in motor symptoms and daily activity scores after DBS surgery.^[20] However, the intensity of stimulation required appears to be higher with general anaesthesia. Ketamine has also been used for DBS surgery and found reliable.^[21]

ANAESTHETIC DRUG EFFECTS ON MICROELECTRODE RECORDING AND MACRO-STIMULATION

Microelectrode recording

The effect of anaesthetic drugs is not homogeneous across different regions of brain and appears to depend

on the specific disease process and target nuclei as well. The amount of gamma-aminobutyric acid (GABA) input to various nuclei influences the degree of effect of anaesthetic drugs. Since the GPi neurons have higher GABA input than STN, GPi neurons are more suppressed by anaesthetic drugs.^[22] Knowledge about anaesthetic drug effects on Vim nuclei is limited.

The subcortical areas of the brain are extremely sensitive to GABA receptor-mediated medications which can result in loss of MER and tremors. Hence, most sedative drugs, especially benzodiazepines, are avoided. Benzodiazepines can abolish tremors as well as interfere with MER and stimulation testing. In addition, respiratory depression and impaired consciousness can occur.

Propofol is the most commonly used anaesthetic agent for DBS surgery. MER, though attenuated, have been successfully recorded from GPi, STN and Vim under propofol anaesthesia.^[23] However, it abolishes tremors, can cause dyskinesia and occasionally, sneezing. Fentanyl or remifentanyl, given minutes before propofol, can avoid sneezing.^[24] In patients with dystonia, propofol has been found to reduce firing rates of GPi nucleus.^[25] Raz *et al.*, in 2008, showed that propofol infusion at 50 µg/kg/min significantly reduced spontaneous firing rate of STN neurons interfering with lead placement, but neuronal activity returned to baseline in 9.4 ± 4.2 min after stopping propofol infusion.^[26]

Desflurane has been successfully used in DBS surgery. MAC level <1 does not impair MER drastically though neuronal firing is attenuated.^[27] MAC >1 has been shown to depress GPi discharges in PD.^[28] MER from STN has been more successful using propofol or dexmedetomidine owing to its lower GABA input.^[29]

Dexmedetomidine due to its non-GABA-mediated action is a good alternative. It has been considered as an ideal sedative agent for DBS surgery due to its ability to produce sedation, anxiolysis, anaesthetic sparing effect, minimal respiratory depression, easily arousable patient and decrease in intracranial pressure. Furthermore, at doses of 0.3–0.6 µg/kg/h, it neither impairs the intensity of movement disorder in PD nor interferes with MER.^[30]

Macro-stimulation

Stimulation testing to see the clinical benefits and adverse effects of DBS is often done but requires an awake and cooperative patient. Patients managed with conscious sedation can also undergo clinical stimulation testing provided short-acting drugs are used and stopped well before testing. General anaesthesia interferes with clinical testing as well as recognition of any adverse effects due to stimulation

of adjacent structures. Use of visual-evoked potential has been described in patients undergoing GPi stimulation under general anaesthesia.^[31] Otherwise, routinely practiced method in patients undergoing DBS surgery in general anaesthesia is to confirm location of electrodes with MRI without any stimulation testing intraoperatively.

COMPLICATIONS

The reported incidence of intraoperative complications varies from 6.9%^[32] to 16%.^[33] Reported complications include coughing, sneezing, bronchospasm, aspiration, airway obstruction, seizure, decreased consciousness, intracranial haemorrhage, pulmonary oedema, agitation, angina, pain, nausea and vomiting and blood loss. The risk of complications increases with bilateral placement of leads. Age has been found to be an independent risk factor for complications.^[34]

Cardiovascular complications

A complication rate of 0.4% is reported.^[34] Complications include angina, congestive heart failure and hypertension. Hypertension due to inadequate pre-operative control, anxiety or secondary to surgical causes commonly occurs intraoperatively and can cause intracranial bleeding. VAE can occur during burr hole making procedure, both in semi-sitting and supine positions. Airway obstruction, deep inspiration and hypovolaemia can contribute to the occurrence of VAE. Awake patients manifest with cough as the initial symptom of VAE followed by tachycardia, tachypnoea, hypotension, hypoxia, etc. Coughing can further aggravate VAE. Maintaining volume status, careful surgical technique and limited head elevation can prevent VAE.

Neurological complications

Death rate of 0.6% has been reported by the American Academy of Neurology in 2006. Seizures, mostly focal and self-limiting, can occur. Generalised seizures can occur and are treated with propofol or benzodiazepine. Anticonvulsants must be readily available. Change in neurological status presenting as confusion, speech or agitation can occur. Tension pneumocephalus due to continuous leak of cerebrospinal fluid from burr holes is possible. Akinetic crisis where the patient is alert and aware, but unable to communicate can occur. Intracranial haemorrhage has a reported incidence of up to 2–4% or 1.4% per lead implant.^[35] It commonly occurs due to poor pre- and intra-operative blood pressure control, coughing, sneezing, coagulopathy, multiple attempts at placing leads, etc. Long-term complications such as depression, hallucinations, mood changes and decreased memory can occur, especially in patients with pre-operative psychiatric illnesses.

Respiratory complications

The incidence of respiratory complications is around 1.1–1.6%.^[33] Airway obstruction is a potential complication and can be devastating, especially in patients under conscious sedation. The presence of head frame, downsliding of the patient on the operating table with the head fixed and neck flexed can further complicate the situation. A clear plan of airway management in case of a catastrophe and presence of emergency equipment is essential.

Position-related side effects

Prolonged nature of surgery and the need to stay immobile or perform repeated mental tasks can cause fatigue in awake patients. Intrathecal hydromorphone,^[36] intraoperative physiotherapy, massage, etc., have been shown to relieve pain and discomfort.

Stimulation-related side effects

Paraesthesias, involuntary movements, mood changes, etc., can occur due to stimulation and can be terminated by stopping the stimulation procedure.

Hardware-related complications

Infection, displacement, lead fracture, pulse generator malfunction, foreign body reaction, etc., can occur and can cause Parkinsonian crisis. Hardware infection rates of 1–15% have been reported.^[10]

Depression

A post-operative incidence of 1.5–25% has been reported.^[37] However, it is difficult to tell if depression occurs due to DBS or due to disease progression. Retrospective studies also show that suicide rates are higher in patients undergoing DBS of STN than in medically treated patients.

Language and speech

Post-operative decrease in verbal fluency and memory problems have been reported.^[38] High-voltage stimulation of left STN has been shown to cause higher risk of speech deterioration.

POST-OPERATIVE COURSE

Patients must be closely monitored post-operatively for neurological deterioration, confusion, etc., Anti-Parkinsonian medications must be started as early as possible but needs to be titrated. Delay can worsen symptoms and cause dystonia and dyskinesia. Nasogastric tube can be inserted and soluble dopa may be given. Analgesics are given as required.

CONCLUSION

The popularity of DBS surgery as a treatment option for various movement disorders is likely to increase as

the number of affected patients increases. An awake or sedated patient is the most suitable for this procedure though no clear-cut evidence exists. Dexmedetomidine appears to be the most suitable agent for sedation of these patients in current clinical practice. Adequate precautions and careful selection of patients can prevent serious complications.

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Conflicts of interest

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