Stimulation of the subthalamic region for essential tremor

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Object. The goal of this study was to determine the safety and efficacy of bilateral subthalamic region stimulation in the treatment of essential tremor (ET).

Methods. Following induction of general anesthesia, four patients with disabling tremor that had proved to be refractory to pharmacotherapy underwent magnetic resonance imaging–guided deep brain stimulation (DBS) of the bilateral subthalamic region. Tremor was assessed by applying the Fahn-Tolosa-Marin Tremor Rating Scale at baseline and again at the 12-month follow-up examination.

Following surgery the total tremor score improved by 80.1% (from a baseline mean score of 63 ± 15.1 to a score of 11.8 ± 3.9 at 12 months postoperatively). There was a significant improvement (p < 0.0001) in the mean tremor score of the upper limb (postural and action component) from a baseline score of 3 ± 0.9 to a score of 0.5 ± 0.5 at 12 months postoperatively. In two patients with Score 4 head tremor complete arrest of the tremor was observed at 12 months. Motor function scores of the upper limb for drawing spirals, pouring water, and drawing lines improved significantly (p < 0.05) by 66.7, 76.9, and 58.3%, respectively. Handwriting improved by 68%, but this gain was not significant. The mean activities of daily living score at baseline was 20 ± 3.2; there was an 88.8% improvement in this score to 2.3 ± 1.5 at the 12-month evaluation. The voltage required for effective tremor control was low (mean 1.8 ± 0.2 V) and, along with the other parameters of DBS (frequency and pulse width), did not change significantly over the 12-month period. Tolerance to the action component of tremor was not seen. There was no procedural or stimulation-related complication.

Conclusions. Bilateral subthalamic region stimulation is effective in arresting tremor and head titubation, as well as functional disability in ET. Complications like dysarthria and disequilibrium were not seen. These patients required low voltages of stimulation and did not develop a tolerance to the treatment.

KEY WORDS • essential tremor • subthalamic region stimulation • deep brain stimulation

Essential tremor is a common movement disorder that occurs in 300 to 415 persons per 100,000 population. The incidence of new cases increases with the age of the person and the disorder is known to affect both men and women equally. Essential tremor has an autosomal-dominant inheritance with variable clinical expression and almost complete penetrance by the age of 65 years.

The cause of ET is poorly understood. Although no morphological changes have been identified, it has been attributed to a functional disturbance in the inferior olivary nucleus, where abnormally synchronized 4- to 12-Hz oscillations occur. These oscillations probably result from excessive electrotonic coupling between the dendrites of inferior olivary neurons via γ-aminobutyric acid–mediated gap junctions. The abnormal oscillations are transmitted via Purkinje cells and the dentate and interpositus nucleus and then distributed to thalamocortical and brainstem nuclei.

Clinical case reports of infarcts or lesions involving these pathways in patients with ET have been shown to arrest tremor.

The inferior olive is thought to play an important role as a “teacher of the cerebellum” in adjusting or modulating planned movements during their execution, in response to unconditioned afferent information. It achieves this by modulating cerebellar return to the motor cortex via the Purkinje cells. Thus in patients with ET, if there is excessive recruitment of inferior olive neurons in response to afferent information and these neurons oscillate synchronously in the 4- to 12-Hz range, a potent effect on motor performance will occur and manifest as tremor.

Drug treatment is effective in only 50% of patients and those whose tremors are refractory to it may be offered stereotactic surgery. Typically the Vim nucleus of the thalamus is the target of choice and lesioning is reported to provide good contralateral tremor suppression. Nevertheless, recurrence may occur within weeks or years, and long-term studies show that significant tremor persists in 17 to 32% of cases. Bilateral lesions are associated with significant complications, including permanent speech impairment in more than 25% and memory and language dysfunction in more than 50% of cases.

Clinical studies indicate that DBS of the Vim is as effective as lesioning in controlling tremor, but DBS is likewise associated with side effects, particularly when performed bilaterally in 30 to 50% of patients suffering from dysarthria and disequilibrium. The adverse effects

Abbreviations used in this paper: ADL = activities of daily living; DBS = deep brain stimulation; ET = essential tremor; MR = magnetic resonance; RN = red nucleus; STN = subthalamic nucleus; Vim = ventralis intermedius; ZI = zona incerta.
associated with DBS, however, are generally reversible by adjusting the stimulation parameters, although this may be at the expense of satisfactory tremor control. Patients treated with DBS have also been reported to develop tolerance (habituation) to stimulation, even when the amplitude is increased. Patients are advised to turn their stimulators off at night and take stimulation holidays for weeks to prevent tissue habituation.2,3,15

Historically, in 1965 Mundinger24 reported good results by making large lesions in the subthalamic region for the control of ET. Subsequently, in 1969 Bertrand and colleagues4 defined an area where the mere impact of the tip of a small probe caused abrupt and total cessation of tremor. This area was in the region of the “prelemniscal radiation” (the most posterior and inferior portion of the ZI, posterodorsal to the STN; the site corresponds to coronal slice FP 7.0 in the Schaltenbrand atlas34).23,40,41 Bertrand and colleagues attributed their findings to lesioning the ascending fibers from the upper mesencephalic reticular substance, the pallidothalamic and pallidotegmental fibers. We now know that this area also carries the dentate– and interpositus–thalamic fibers on the way to the Vim. Subsequently, long-term follow-up studies of lesions involving the ventral thalamus and the subthalamic region showed an improvement in ET with a low complication rate. Hypotonia and gait disturbance were observed in 5% and speech disturbance in 1% of patients.23 Kitagawa, et al.,17 have recently reported two cases of severe proximal ET in which good results were attained by stimulating the subthalamic fibers from the upper mesencephalic reticular substance, the pallidothalamic and pallidotegmental fibers. We now know that this area also carries the dentate– and interpositus–thalamic fibers on the way to the Vim. Subsequently, long-term follow-up studies of lesions involving the ventral thalamus and the subthalamic region showed an improvement in ET with a low complication rate. Hypotonia and gait disturbance were observed in 5% and speech disturbance in 1% of patients.23 Kitagawa, et al.,17 have recently reported two cases of severe proximal ET in which good results were attained by stimulating the subthalamic region including the ZI.

Four patients with ET were included in our pilot study and underwent DBS of the subthalamic region for tremor control; we now report the 12-month follow-up results in these patients.

Clinical Material and Methods

Patient Population

Four patients (three women and one man) who were examined in the senior author’s (S.S.G.) clinic for functionally disabling ET (postural or intention tremor of the hands and forearm or an isolated head tremor without evidence of dystonia, and also absence of other neurological signs except cogwheeling), despite maximum pharmacological therapy (up to 320 mg propranolol and as much as 750 mg primidone) were considered candidates for surgery and were included in this pilot study. The mean age of the patients was 66.8 ± 8.5 years. The mean duration of the disease for the women was 10.3 ± 1.5 years; the sole male patient had ET for 38 years. A positive family history of ET was found in all patients. Every patient gave fully informed consent and was aware of the potential risks of stereotactic surgery.

Clinical Evaluation

All patients were assessed by applying the Fahn-Tolosa-Marín Tremor Rating Scale.25 This scale is divided into Parts A, B, and C. Part A (Items 1–9) is used to quantify the tremor at rest, with posture holding and with action and intention maneuvers to the various body parts. Part B (Items 10–14) deals with action tremors of the upper extremities, particularly as they relate to writing and pouring liquids. Part C (Items 15–21) is used to assess functional disability with ADL (eating solids, drinking liquids, hygiene, dressing, writing, and working). Voice tremor was evaluated by listening to the patient talk and assessing the ability to utter a single sound such as “aaahhh” and hold it for as long as possible. Scores are based on a five-point scale (Score 0, no tremor; Score 1, slight tremor [amplitude < 0.5 cm], may

FIG. 1. Left: High-resolution axial T2-weighted MR image demonstrating the delineated STN, RN, and the mamillothalamic tracts (MTs). Right: Preoperative high-resolution coronal T2-weighted MR image demonstrating the outlined head of the caudate nucleus (CD), thalamus (TH), STN, and substantia nigra (SN).
be intermittent; Score 2, moderate tremor [amplitude 0.5–1 cm], may be intermittent; Score 3, marked tremor [amplitude 1–2 cm]; and Score 4, severe tremor [amplitude > 2 cm]). Evaluations were performed preoperatively and at 12 months postoperatively by a specialist movement disorder nurse. Preoperative assessments were performed after withholding medication (propranolol and primidone) for 12 hours overnight. Postoperative assessments were performed with the patient in two states: with the stimulator switched off for 3 hours and, subsequently, with the stimulator switched on.

Magnetic Resonance Imaging and Target Planning

Approval from the ethics committee was obtained to perform stereotactic procedures following induction of general anesthesia by using implantable guide tubes to deliver the electrodes. Each guide tube was an in-house investigational device (Ansamed Ltd., Rosscommon, Ireland). After induction of general anesthesia, a modified Leksell stereotactic frame (Elekta Instruments AB, Stockholm, Sweden) was affixed parallel to the orbitomeatal plane. Patients then underwent high-resolution MR T2-weighted imaging sequences (1.5-tesla imager, TR 2500 msec, TE 150 msec, turbo–spin echo factor 11, number of signal averages 12) to define the STN and the RN. The anterior and posterior commissures were identified on a midsagittal planning image. Axial 2-mm-thick images were acquired parallel to the anterior commissure–posterior commissure plane and coronal images orthogonal to these. Magnified hard copies of the T2-weighted images were obtained and overlaid onto inverted T2-weighted images to enhance further the definition of the STN and surrounding structures. The boundaries of the STN, RN, and related structures were outlined and a three-dimensional volume was created by cross-correlating the boundaries on the axial and coronal images (Fig. 1). The target area in the subthalamic region was then defined in relation to the STN, ZI, ventral thalamus, RN, and medial lemniscus by using the Schaltenbrand atlas as a visual guide. The target area was medial to the posterior dorsal third of the STN, an area encompassing the ascending dentate–and interpositus–Vim fibers and part of the ZI. The trajectory was planned, traversing the target such that the third proximal contact on the DBS electrode (Contacts 2 and 6) would be positioned at the planned target site and the distal end of the electrode placed deeper in the subthalamic region.

Surgery and Target Verification

Surgery was performed while the patient was in a state of general anesthesia and placed semisitting so that the frontal burr holes were uppermost. This ensured that with constant saline irrigation and avoidance of air entry, brain shift would be minimized. A probe was inserted into the target and over this a plastic guide tube was advanced so that its distal end fell short of the target by several millimeters. The proximal end of the guide tube, which is in the form of a hub, was bonded within the burr hole with acrylic cement. The probe was then withdrawn and replaced with a plastic stylette (in-house investigational device; Ansamed Ltd.) cut into an appropriate length so that its distal end traversed the target to a planned position in the subthalamic region (Fig. 2 left). This procedure was carried out bilaterally. The patient then underwent intraoperative MR imaging to verify the position of the plastic stilettes relative to the planned target (Fig. 3). On confirmation of satisfactory placement, the patient was returned to the operating room and the frame was removed. The plastic stilettes were also removed and replaced with DBS leads (models 3387 and 3389; Medtronic, Inc., Minneapolis, MN) (Fig. 2 right). The leads were secured to the skull with miniplate and screws, and then connected to extension cables and the DBS pulse generator (Kinera; Medtronic, Inc.). The pulse generator was implanted into a subcutaneous pocket below the clavicle. The whole procedure typically took 3.5 to 4 hours, including intraoperative imaging and implantation of the DBS device.

Postoperative Management

The Kinera generator was switched on immediately after surgery. In the following days it was programmed by the movement disorder nurse, who optimized tremor control in all patients after programming all four DBS contacts. The specialist nurse was blinded, however, to the optimal planned DBS contact. Patients were advised to stop their antitremor medications gradually over the coming weeks.

Statistical Analysis

Primary efficacy was analyzed using the paired Wilcoxon signed-rank and sign test. The test of significance was applied to the scores of the affected extremity, functional activities of the upper limb, and also the ADL.

Results

Part A Scores

The total tremor score at 12 months after surgery im-
proved by 80.1% (from a baseline mean score of 63 ± 15.1 to a score of 11.8 ± 3.9 at 12 months postoperatively). The Part A score (Items 1–9) improved by 84.2% (from a baseline mean score of 19 ± 4.4 to a score of 3 ± 1.2 at 12 months postoperatively; Fig. 4). All patients had severe tremor in both upper limbs (mean postural tremor score 3 ± 0.9, mean action tremor score 3.4 ± 0.7), although one patient also had rest tremor with no bradykinesia or rigidity. Following DBS implantation, the tremor was completely arrested in five of eight upper limbs and a Score 1 tremor was seen in the remainder. This was reflected in an overall improvement in the combined posture and action component tremor scores by 84.4% (from a mean baseline score of 3.2 ± 0.8 to a score of 0.5 ± 0.5 at 12 months postoperatively; p value < 0.0001; Table 1). A Score 4 head tremor was seen in two patients, which disappeared completely at 12 months. One patient had both facial and voice tremor, with the former disappearing completely and the latter showing a marked improvement.

Part B Scores

The Part B score (Items 10–14) improved by 67% (from a baseline mean score of 24.3 ± 7.5 to a score of 8 ± 1.2 at 12 months postoperatively; Fig. 4). The ability to draw spirals, draw lines, and pour water improved significantly (p < 0.05) by 66.7, 58.3, and 76.9%, respectively. Handwriting showed a 68% improvement; however, this was not found to be a significant change (p > 0.05). Because the most disabling tremor for patients with ET is the postural and action upper-limb tremor, we calculated the improvement for this category by summing the postural and action tremor scores of the upper limb with the motor score related to functional activities of the upper limb (writing, drawing, and pouring). This category improved by 75.2% following surgery (Table 1).

Part C Scores

Part C scores (Items 15–21) improved by 88.8% (from a mean baseline score of 20 ± 3.2 to a score of 2.3 ± 1.5 at 12 months postoperatively). Individual tasks of daily living (eating solids, drinking liquids, hygiene, dressing, writing, and working) also showed marked improvements (Table 2).

Global Disability Assessment

Before surgery two patients described themselves as being severely disabled (75–100% impairment) and two as markedly disabled (50–75% impairment), based on the global disability assessment (scored by both the patient and the physician) as part of the clinical tremor rating score.13 One year following surgery three patients had no functional disability and one had mild disability (1–25% impairment).
rather than nuclei. We therefore adopted an image-directed
method by using high-resolution and long-acquisition T2-
weighted MR images to identify the target site.

In the immediate vicinity of our planned target are a num-
ber of anatomical structures that could potentially influence
tremor including the Vim, ZI, and STN. Therefore, accurate
identification of the position of the most effective contact
was essential. Unfortunately, postoperative MR imaging of
DBS electrodes to identify the anatomical locations of indi-
vidual contacts is hampered by a metal artifact that distorts
the images. To overcome this we used the guide tube method
described earlier.

The guide tube with an indwelling stylette acts as a de-
vice that enables neuroimaging confirmation of the optimal
target localization. Following implantation, the guide tube
effectively fixes the brain target and the stylette can be in-
serted down the guide tube into the target. Intraoperative vi-
sualization of the stylette will identify precisely where the
DBS lead will subsequently be placed and, in turn, where
each contact will be anatomically positioned. If placement
of the stylette is suboptimal, this can be identified and the
DBS lead position can be adjusted appropriately. This tech-
nique is safe and accurate and allows us to perform all func-
tional neurosurgery cases during general anesthesia.

Patient Outcome

The total tremor score improved by 80.1%: Part A by
84.2%, Part B by 67%, the functional motor score for the
upper limb by 75.2%, and Part C by 88.8%. This improve-
ment can be compared with the findings of a multicenter
European study in which 37 patients underwent either uni-
lateral or bilateral thalamic stimulation for ET. In that study
there were also significant (p < 0.05) improvements: Part
A scores improved by 55%, Part B by 43.9%, and Part C

| TABLE 2 |

<table>
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<th>Factor</th>
<th>Eating Solids</th>
<th>Drinking Liquids</th>
<th>Hygiene</th>
<th>Dressing</th>
<th>Writing</th>
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<td>3.0 ± 0.8</td>
<td>4.0</td>
<td>3.5 ± 0.6</td>
<td>2.3 ± 1.0</td>
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<td>3.0 ± 0.8</td>
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<td>DBS turned on</td>
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<td>0.5 ± 0.6</td>
<td>0.0</td>
<td>0.3 ± 0.5</td>
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* Scores are given as means ± SDs.
by 80.3%. In another series of nine patients with ET who underwent staged bilateral thalamic stimulation, Pahwa, et al., showed that the total tremor scores improved by 57%, the functional motor score of the upper limb by 65%, and the Part C score by 57%.

In our series, head and face tremor was completely arrested and a marked improvement was noted in voice tremor, when present. In comparison, in their series, Taha and associates reported a greater than 50% improvement in head tremor in eight of nine patients, with no complete arrest reported. All but one patient underwent bilateral DBS. One patient had multiple sclerosis. Our results, based on two patients, may indicate that bilateral subthalamic region stimulation can effectively control axial tremor.

**Tolerance and Pulse Generator Parameters**

Benabid and colleagues reported tolerance to Vim stimulation. Tolerance to particular stimulation parameters may occur after days or weeks and a regular increase in stimulation intensity is necessary to maintain control. Even at a maximally tolerable intensity, tremor may still break through and, in these circumstances, it is necessary to stop the stimulation for a variable period (stimulation holiday). Clinicians at most centers advise turning the stimulator off at night to postpone the appearance of tolerance. Benabid, et al., found that 18.5% of 22 patients developed tolerance within 3 to 6 months, with the action component of tremor being more susceptible than the rest tremor. In our series tolerance was not seen, despite the fact that constant stimulation was maintained. Excellent tremor control of both the postural and action component was achieved in all patients with complete tremor arrest in five of eight sides and Score 1 tremor in three of eight sides. The original stimulation parameters were not significantly changed and the voltage remained low (mean 1.8 ± 0.1 V). Published reports have shown a higher mean initial voltage, which increases with time to optimize tremor control, especially the action component.

We attribute our findings of good tremor control at low voltage to the fact that we targeted the ascending dentate–and interpositus–thalamic fibers where they are confined to a small volume in the subthalamic region. This contrasts with the relatively large wedge-shaped volume of the Vim that would be necessary for stimulation to achieve the same effect (Fig. 5). The low voltage may also be attributed to the fact that axonal tracts are more susceptible to high-frequency stimulation than are neuronal bodies as in the Vim.

**Stimulation-Related Complications**

Stimulation-related side effects with bilateral Vim DBS include dysarthria and disequilibrium, which are reported in as many as 30 to 50% of cases in some series. To avoid these side effects, many surgeons have resorted to unilateral or staged bilateral procedures. In our small surgical series, in which patients underwent simultaneous bilateral insertion of DBS electrodes, we have had no procedure- or stimulation-related side effects.

**Conclusions**

Essential tremor is a fairly common movement disorder, especially in the elderly population. It can be functionally disabling and medically refractory in a high percentage of patients. Bilateral Vim stimulation is associated with a high complication rate. Subthalamic region stimulation deserves further consideration as a potential target for the effective control of both distal and axial tremor.

**Acknowledgments**

We thank Paul Bodenham and Ruth Spencer for the illustrations.

**References**


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* Values are expressed as means ± SDs.

**FIG. 5.** Schematic diagram showing the position of the DBS electrode in relation to the path of the cerebello–Vim fibers from the dentate and interpositus nuclei on the left side. The electrode is placed where these fibers are concentrated together in the subthalamic region before “fanning out” to the large body of the Vim above. Cd = caudate nucleus; GPi = globus pallidus internus; IC = internal capsule; PUT = putamen.