Long-term results of thalamic deep brain stimulation for essential tremor

Clinical article

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Object. Deep brain stimulation (DBS) of the ventral intermediate nucleus of the thalamus (VIM) has proven to be efficacious in the treatment of essential tremor (ET). The authors report on long-term follow-up of a series of patients treated at 1 institution by 1 neurosurgeon.

Methods. Thirty-four patients with ET received unilateral or bilateral VIM DBS. The tremor and handwriting components of the Fahn-Tolosa-Marin clinical tremor rating scale were assessed pre- and postoperatively. Visual analog scale scores for overall patient satisfaction and tremor control were recorded. Stimulation parameters at different intervals after surgery were also recorded.

Results. The average follow-up period was 56.9 months. The average tremor score improved from 3.27 preoperatively to 0.64 postoperatively (on stimulation; p < 0.001) and the average handwriting score improved from 2.94 to 0.89 (p < 0.001). The average visual analog scale score for overall satisfaction was 8.12 and for tremor control was 1.43. Overall, there was an 80.4% improvement in tremor and 69.7% improvement in handwriting. In 12 patients both tremor and handwriting scores were compared between 57.3 months and 90.7 months after surgery and no significant changes were discovered. Comparison of stimulation parameters at onset and at 1–3, 3–5, 5–7, and > 7 years after surgery showed significant differences, with a gradual increase in stimulation parameters within 5 years after surgery. The overall hardware-related complication rate was 23.5%.

Conclusions. Deep brain stimulation of the VIM is an efficient and safe treatment for ET. Tremor and handwriting improvements in long-term follow-up are stable. The patients’ perception of their outcome is quite good. However, tolerance may develop in some patients requiring changes in stimulation parameters.

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Key Words • essential tremor • deep brain stimulation • thalamus • handwriting • visual analog scale • ventral intermediate nucleus

Essential tremor is one of the most common adult movement disorders. Its prevalence is as high as 4% according to a recent large population-based survey.22 Because the pathogenesis of ET remains poorly understood, the development of innovative pharmacotherapeutic treatments is greatly hindered. Options for drug therapy include the use of primidone, beta-adrenergic blockers (such as propranolol), alcohol, benzodiazepines, gabapentin, carbolic anhydrase inhibitors, clozapine, flunarizine, clonidine, and the methylxanthine-derivative theophylline.8 Although there are abundant medications, few are effective in controlling severe tremor. The introduction of DBS in 1987 brought about a renaissance of surgical treatment for ET.3 Currently, stimulation of the VIM has become the standard treatment in tremor-disabled patients with ET. Although VIM DBS has proven to be safe and effective in ET,1,12,16 most published studies report relatively short-term results while its long-term efficacy is less commonly reported. In this study we retrospectively analyze data collected in a consecutive series of patients with ET from a single-institution, single-surgeon perspective. Our aim is to analyze the long-term efficacy and safety of VIM DBS in ET.

Methods

Patient Selection

A consecutive series of 34 patients with ET received unilateral or bilateral VIM DBS between January 1998 and
October 2005 at Allegheny General Hospital by 1 neurosurgeon (D.W.). All patients suffered from disabling tremor despite adequate pharmacological treatment. Tremors included resting, positional, and action tremor during waking hours. Patients who presented with psychiatric disease, dementia, depression, and other neurological disorders were excluded. The study was approved by the Institutional Review Board as a retrospective review of prospectively collected data.

Surgical Procedure

The surgical technique used for VIM DBS has been described elsewhere.\(^4\) In brief, preoperative planning was performed using either CT or MR imaging/CT fusion. Software provided by the Stim-Pilot system (Medtronic Inc.) was used for targeting and microelectrode recording. Surgery was performed in 1 stage until the end of 2001 and in 2 stages thereafter. On the morning of the surgery a Cosman-Roberts-Wells frame (Integra Radionics) was placed on the patient’s head and a CT scan was obtained. This scan was fused with the existing MR imaging scan and coordinates of the VIM and the trajectory were calculated. Microelectrode recordings were used to confirm the location of the VIM. The DBS electrode (model 3389, Medtronic Inc.) was then implanted. The clinical efficacy as well as side effects of macrostimulation was assessed. The electrode was secured to the bur-hole attachment by a locking device and a bur-hole cap using the Stimlock system (Medtronic, Inc.). The intermittent pulse generator was connected to each DBS electrode through an extension wire and placed in the infraclavicular region immediately (1 stage) or 1 week after the first surgery (2 stage).

Unilateral implantation was the standard protocol until the end of 2001, with the electrode implanted in the VIM contralateral to the dominant side. Bilateral systems were chosen in some cases thereafter, based on the patient’s symptoms.

Follow-Up and Postoperative Evaluation

The stimulators were usually turned on 3 weeks after the implantation of electrodes. During the first several postoperative months, the parameters were adjusted to get optimal control of tremor without side effects. Further minor adjustments of polarities and other parameter settings were made thereafter, if needed. Follow-up was performed at routine visits, usually every 3–6 months. Efficacy, parameters, and complications of VIM DBS were recorded at each follow-up visit. The battery was replaced when the charge was measured to be < 3.6 V. Besides the routine follow-up, patients were contacted by telephone for comprehensive evaluation of therapeutic efficacy in February 2006 and December 2008. At these times, the tremor and handwriting components of the Fahn-Tolosa-Marin clinical TRS\(^*\) were assessed. Visual analog scale scores for overall patient satisfaction (0 = not satisfied, 10 = extremely satisfied) and tremor control (0 = no tremor, 10 = maximum tremor) were also recorded. In patients with bilateral VIM implantation, TRS and VAS tremor scores were evaluated on both sides and handwriting score was evaluated on the dominant side. Scores of both stimulation-off and stimulation-on state were evaluated. Stimulation parameters were collected at each visit if a reprogramming was performed; these parameters included polarity, amplitude, frequency, and pulse width. All tests were performed by a trained nurse who was a disinterested observer.

Data Collection and Statistical Analysis

Demographic data (sex, age, duration of disease, and preoperative symptoms) were collected. At the time of the February 2006 and December 2008 comprehensive reevaluation, some patients had died or had otherwise dropped out. For these patients, Fahn-Tolosa-Marin TRS scores at the last follow-up were compared with measurements before surgery. For all other patients (who received both the 2006 and 2008 reevaluation), Fahn-Tolosa-Marin TRS scores were compared between these 2 time points to evaluate the outcome stability. Due to nonnormal distribution of outcome measures, pre- and poststimulation scores were compared statistically using the Wilcoxon signed-rank test. According to the time after implantation, stimulation parameters were divided into initial parameters, and those recorded 1–3, 3–5, 5–7, and > 7 years after surgery. These parameters were compared statistically using 1-way ANOVA. A probability value < 0.05 was considered statistically significant. Statistical software SPSS (version 16.0, SPSS Inc.) was used for statistical analysis.

Results

Demographic Data

Of the 34 patients, there were 23 men and 11 women. The average patient age was 58.3 ± 12.8 years (range 34–83 years). The average duration of ET prior to surgery was 22.1 ± 13.1 years (range 4–50 years; Table 1). The sides of implantation and the locations of symptoms are also listed in Table 1. Of the 34 patients, 4 died, and 2 had their implantation systems removed due to infection/erosion of incision.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
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<tbody>
<tr>
<td>mean age in yrs (± SD)</td>
<td>58.3 ± 12.8</td>
</tr>
<tr>
<td>M/F</td>
<td>23 (67.6):11 (32.4)</td>
</tr>
<tr>
<td>mean duration of ET in yrs (± SD)</td>
<td>22.1 ± 13.1</td>
</tr>
<tr>
<td>placement of stimulator</td>
<td></td>
</tr>
<tr>
<td>lt</td>
<td>22 (64.7)</td>
</tr>
<tr>
<td>rt</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>bilat</td>
<td>11 (32.4)</td>
</tr>
<tr>
<td>location of symptoms</td>
<td></td>
</tr>
<tr>
<td>arms</td>
<td>12 (42.9)</td>
</tr>
<tr>
<td>arms &amp; head</td>
<td>8 (28.6)</td>
</tr>
<tr>
<td>arms, voice, head</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>arms &amp; voice</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td>arms, legs, head</td>
<td>2 (7.1)</td>
</tr>
</tbody>
</table>

* Data expressed as number of patients (%) unless otherwise indicated.
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There were 22 patients who presented in February 2006 and 12 in December 2008 for reevaluation (Fig. 1). Patients dropped out of the reevaluations due to miscellaneous reasons (2 ceased to use the system due to side effects, 3 moved to other states, 3 developed serious comorbidities, 5 lost contact, and 3 were doing well but did not want to come). However, we kept in contact with most patients by regular programming, generator replacement, or telephone visit, thus their complications and stimulation parameters were still recorded. The average follow-up period of the whole series was 56.9 months (range 3–128 months). Twelve patients received their reevaluation in both February 2006 and December 2008. In this subgroup, the average follow-up period in 2006 and 2008 was 57.3 months and 90.7 months, respectively.

Surgical Efficacy

Of the 34 patients, the mean preoperative Fahn-Tolosa-Marin TRS tremor score was 3.27 ± 0.87. At their last follow-up evaluation, the mean TRS tremor score was 3.18 ± 0.87 in the stimulation-off state and 0.64 ± 0.75 in the stimulation-on state (Fig. 2). There was a significant difference between preoperative and postoperative stimulation-on scores (p < 0.0001), as well as between postoperative stimulation-off and stimulation-on scores (p < 0.0001), while there was no significant difference between preoperative and postoperative stimulation-off scores (p = 0.381). The mean preoperative Fahn-Tolosa-Marin TRS handwriting score was 2.94 ± 0.91. At the last follow-up evaluation, the mean handwriting score was 2.76 ± 1.17 with stimulation off and 0.89 ± 0.91 with stimulation on (Fig. 2). There was a significant difference between preoperative and postoperative stimulation-on scores (p < 0.0001), as well as between postoperative stimulation-off and stimulation-on scores (p < 0.0001), while there was no difference between preoperative and postoperative stimulation-off scores (p = 0.161). At the last follow-up, the average VAS score for patient satisfaction was 8.12 ± 2.51 and for tremor control was 1.43 ± 2.62.

To explore the long-term efficacy of VIM DBS for ET, we analyzed data in the subgroup of patients who received both the February 2006 and December 2008 reevaluation. Twelve patients were eligible in this subgroup. For the 22 patients assessed in 2006 the stimulation-off tremor score was 3.00 ± 0.88 and the stimulation-off handwriting score was 2.50 ± 0.97. With the stimulation on the tremor score improved to 0.33 ± 0.49 and the handwriting score improved to 0.70 ± 0.68.

For the 12 patients assessed in 2008 the stimulation-off tremor score was 3.33 ± 0.72 and the stimulation-off handwriting score was 2.80 ± 1.32. With the stimulation on the tremor score improved to 0.67 ± 0.72 and the handwriting score improved to 1.30 ± 1.16. There was no difference in the probability values among the scores over time, indicating stable and lasting improvement (Table 2).

Stimulation Parameters

After surgery, the stimulation parameters were usually set at a relatively modest level. These parameters were then increased gradually to assure optimal benefits and avoid side effects. Most of the patients in our series were stimulated in the bipolar mode initially to produce a more localized effect. The unipolar mode was chosen as the alternative when bipolar stimulation with various parameter combinations failed. The intensity of stimulation usually went down to prevent side effects when the polarity changed due to the more robust and diffuse effect of unipolar stimulation.

The mean polarity, voltage, frequency, and pulse

### Table 2: Comparison of Fahn-Tolosa-Marin TRS tremor and handwriting scores in stimulation-on and -off states at different follow-up intervals

<table>
<thead>
<tr>
<th>Component</th>
<th>Mean Score</th>
<th>2006</th>
<th>2008</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>stimulation-off tremor</td>
<td>3.00 ± 0.88</td>
<td>3.33 ± 0.72</td>
<td>0.10</td>
<td></td>
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<tr>
<td>stimulation-on tremor</td>
<td>0.33 ± 0.49</td>
<td>0.67 ± 0.72</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>stimulation-off handwriting</td>
<td>2.50 ± 0.97</td>
<td>2.80 ± 1.32</td>
<td>0.48</td>
<td></td>
</tr>
<tr>
<td>stimulation-on handwriting</td>
<td>0.70 ± 0.68</td>
<td>1.30 ± 1.16</td>
<td>0.10</td>
<td></td>
</tr>
</tbody>
</table>

* No significant difference existed in all components.
width at various intervals after surgery are listed in Table 3. Parameters at initial programming and at 1–3, 3–5, 5–7, and > 7 years after surgery were compared. In general there was a significant difference in all parameters including voltage (p = 0.002), frequency (p = 0.028), and pulse width (p = 0.04). Within 5 years after surgery, there was an overall increasing trend in all 3 parameters, with the parameters at 1–3 years significantly higher than the initial ones (p < 0.05), whereas there was no statistically significant difference between the 1–3 and 3–5 year parameters.

Adverse Events and Complications

Adverse events usually observed during postoperative programming included tingling, numbness of an extremity, eye movement disorders, weakness, gait instability, slurring of speech, and drooling. Usually these symptoms disappeared with changes in stimulation parameters. However, 2 patients who initially received benefits from VIM DBS ceased to use the system because of persistent severe paraesthesias, which did not respond to changes in stimulation parameters.

Hardware-related complications included skin erosions (occurring in 2 patients, treated with incision and debridement), overt infections (occurring in 3 patients; the whole system was explanted in all and reimplemented several months later in 1 patient), lead fracture (occurring in 4 patients and all had their lead replaced), and connection cable malfunction (occurring in 1 patient, in whom the cable was replaced). These complications occurred in 8 patients, and the overall hardware-related complication rate was 23.5%.

Discussion

The predominant symptoms of ET include action tremor of the arms and hands, head, and possibly voice. Mild tremor can often be controlled with medication, but approximately 10% of patients suffer from severe disability. For patients with significant tremor that is not controlled adequately by medication, surgical intervention is the optimal solution. Two methods, thalamotomy and VIM DBS, have been widely used and the latter is now more widely accepted due to its high efficacy and safety.

Many studies have established the efficacy of VIM stimulation for the symptomatic treatment of ET or the tremor associated with Parkinson disease. However, its long-term efficacy is relatively less often reported. Table 4 lists the recent studies involving long-term follow-up of VIM DBS in the treatment of ET. Our results are consistent with most of these data. In our study, we noted statistically significant improvements in both the tremor and handwriting components of the Fahn-Tolosa-Marin clinical TRS at the last follow-up, which averaged 56.9 months. The VAS scores, which measured patients’ contentment with the procedure and their perception of tremor control, indicated a high degree of overall satisfaction and tremor control. Moreover, in a subgroup of 12 patients who received reevaluation after a mean of 57.3 and 90.7 months after surgery, there was no significant difference in Fahn-Tolosa-Marin TRS tremor and handwriting scores between the 2 intervals. The above results strongly support the idea that thalamic stimulation for ET retains its positive effects over long-term follow-up.
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as judged both by the clinician and the patient. The fact that the reductions observed in the tremor and handwriting scores in the postoperative stimulation-off state were small demonstrates that the contribution of a microthalamotomy effect to the overall results was minimal. Adding to the strength of these results is the fact that all of these procedures were performed at a single center by the senior surgeon, leading to uniformity in patient selection and technical aspects of the procedure.

In our study, stimulation parameters gradually increased within 5 years after surgery, with the 1–3 year parameters significantly higher than the initial ones (p < 0.05). Other reports have also shown similar results.5,7,18 After 5 years, the parameters fluctuated in our patient series, chiefly caused by mode change, in which we used unipolar stimulation as an alternative to bipolar stimulation. Parameters were usually decreased after 5 years because the unipolar stimulation was more robust and more likely to cause side effects otherwise. Our average stimulation parameters 7 years after surgery were voltage 3.2 V, frequency 168.3 Hz, and pulse width 90 msec. These parameters are higher than some other reported parameters, but still comparable to most other reports.5,17,18,20,21

In our study, there were 2 patients who initially received excellent benefit from VIM stimulation with usual stimulation parameters but eventually ceased to use the system because of persistent paraesthesias. This stimulation failure has also been observed in other studies.18 Usually, there are 2 groups of stimulation failure, those who receive no benefit immediately after surgery and those who initially received good benefit initially but gradually note a return of their tremor. The former is believed to be caused by suboptimal location of target and can usually be treated by reimplantation of the stimulator. The latter situation is more complicated. Two underlying rationales have been proposed: progression of the ET and tolerance. The role of disease progression is debatable. The slowly progressive characteristics of ET and relatively stable stimulation-off symptoms even several years after surgery make this idea less reasonable. Tolerance is not uncommon in the long-term follow-up of DBS in the treatment of Parkinson disease and ET.5,7,10,18 In fact, most authors notice a gradual increase of voltages during postoperative long-term programming, which is believed to be partly caused by tolerance. There has been no solution to this problem, yet lower voltage settings and intermittent usage of the stimulator (usually turning the stimulator off during sleeping hours) might help to some extent.5 A thalamotomy is also an option for those who experience tolerance.

Hardware complications are common and bothersome after DBS surgery. The complication rate varied between 6.7% and 49% in different reports and often required additional surgery as a result.5,11,14,15 In our series, the hardware-related complication rate was 23.5%. The hardware-related complication rate fell significantly after 2003.4 Our rates are similar to those mentioned in the literature and have shown a significant decline over time. We believe that technical and hardware-related improvements as well as surgeon experience are the key factors in lowering complication rates of DBS.

Conclusions

Thalamic DBS is an efficient and safe treatment for ET. Long-term follow-up shows a stable and durable relief of tremor in most patients. The outcome was also quite good from the patient’s perspective. Most side effects were transient and reversible. The overall complication rate was low and acceptable. However, tolerance and loss of efficacy may be observed in some patients and should be taken into consideration.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

References