Thalamic deep brain stimulation for the treatment of tremor due to multiple sclerosis: a prospective study of tremor and quality of life

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Object. In several studies a significant reduction in tremor after thalamic deep brain stimulation (DBS) has been reported among patients with multiple sclerosis (MS). It has not been determined if this results in an improved quality of life. In this study the authors prospectively evaluated the effects of thalamic DBS on tremor and quality of life.

Methods. Videotapes of the patients’ tremor were made preoperatively and 2 and 12 months postoperatively, and tremor was scored by a neurologist blinded to the treatment. Patients were tested pre- and postoperatively to measure any changes in their reported ability to perform selected activities of daily living and in their health-related quality of life. Patients were asked to complete a questionnaire about their satisfaction with the surgery. Postoperative changes were examined using paired t-tests.

There were significant reductions in postural, action, and overall tremor at 2 and 12 months postoperatively. The patients’ reported ability to feed themselves was significantly improved 2 months after surgery (p = 0.01). There were short-term trends toward improvement in reported dressing ability, personal hygiene, and writing. There were no significant changes in the SF-36 subscales or total score.

Conclusions. In this cohort of patients with MS who suffered from tremor, thalamic DBS significantly improved their tremor and ability to feed themselves. Patient satisfaction with the procedure, however, was variable. Preoperative patient education about what functions might (and might not) be improved is crucial to avoid unrealistic expectations. Our results indicate that younger patients with MS tremor who had a shorter disease duration and no superimposed ataxia benefited most from this surgery.

KEY WORDS • multiple sclerosis • tremor • thalamus • deep brain stimulation • stereotactic neurosurgery • quality of life

Tremor of varying severity is estimated to occur in 75% of patients with diagnoses of MS. Although frequently embedded in a complex of other neurological symptoms, it can be the most disabling. There are no published quantitative studies documenting the contribution of tremor to the level of disability caused by MS, but it is well recognized that tremor can decrease the quality of life by interfering with many ADLs such as feeding, drinking, and hygiene. To date, several drugs have been tested but unfortunately none have produced a significant improvement in tremor. The reduction in tremor reported following stereotactic thalamotomy has been offset by complications, and this treatment remains controversial. Chronic DBS of the ventral intermediate nucleus of the thalamus has been reported to reduce MS-related tremor significantly.

The DBS technique has the advantage of being adjustable postoperatively (to maximize benefits and avoid complications) and the procedure produces minimal neural damage. Previous surgical series for tremor in MS focused on the amount of tremor reduction, but none mentioned whether this symptom reduction resulted in improved quality of life. If tremor is statistically reduced but patients are no better able to perform their ADLs, one may question the value of the procedure. This study was designed to evaluate prospectively the effects of thalamic DBS on both tremor and quality of life in patients with tremor due to MS.

Clinical Material and Methods

Patient Selection

Twelve patients with MS who were referred to the Surgical Centre for Movement Disorders at the University of British Columbia were prospectively entered in the study. There were seven women and five men whose mean age was 34.5 years (range 28–42 years). The Surgical Centre for Movement Disorders is the only referral center for functional and stereotactic neurosurgery in the Province of British Columbia (> 4 million people). All patients had received diagnoses of clinically definite MS according to the criteria defined by Poser, et al. One had primary progres-
sive MS, 10 had secondary progressive MS, and one had relapsing–remitting disease. Patients were selected if they had limb weakness or numbness that would render their arm useless despite reduced tremor, or reduced cognition that would interfere with cooperation during surgery or informed consent. All procedures were unilateral (eight on the left and four on the right side). One patient developed an infection that required explantation of the hardware (see Postoperative Complications) and was omitted from the study.

Surgical Procedure

Patients were admitted on the morning of surgery. A head frame (CRW; Radionics, Burlington, MA) was attached to the skull after application of a local anesthetic, and a localizing computerized tomography scan was performed with the frame bolted to the gantry. We preferred computerized tomography scanning over magnetic resonance imaging because a slight head tremor can blur the magnetic resonance images. Initial coordinates for the electrode target were selected at the level of the AC–PC line, 10 mm lateral to the edge of the third ventricle and one quarter to one third of the distance from the PC to the AC.

Patients received preoperative antibiotic drugs intravenously (1 g cefazolin; Novopharm, Toronto, ON) on transfer to the operating room. The anesthetist was instructed to avoid sedating the patient and to maintain normotension, because sedation can interfere with patient communication and reduce intraoperative tremor. The patient’s head was shaved over the coronal suture and the scalp was prepared, draped, and infiltrated with a local anesthetic agent. After one patient developed a wound infection, we switched from the thalamus. The ventral intermediate nucleus target, located just anterior to the sensory nucleus, was selected when stimuli (0.7–1.3 V, 1-msec square waves at 50 Hz) produced paresthesia in the affected limb (ideally in the thumb). The target was confirmed when placement of the probe produced a microthalamotomy effect, or high-frequency stimulation (1–2 V, 0.1 msec, 180 Hz) blocked the tremor.

Once the probe had found the target area, it was replaced by a quadripolar DBS lead (model 3387-40; Medtronic, Minneapolis, MN) under fluorescent guidance. The lead was locked in place with a burr-hole button and the scalp was temporarily closed. Early in our experience, placement of the IPG (Iret II, model 7424; Medtronic) was often performed several days later. Patients with a temporary external extension from the DBS lead to a handheld pacemaker (model 3628; Medtronic) were monitored for their response to a variety of stimulation settings. If a good response was confirmed, we would then proceed with implantation of the IPG. More recently, we have been combining the two procedures after intraoperative confirmation of target localization.

During insertion of the IPG, patients received a general anesthetic agent. This stage of the procedure involved making a subcutaneous pocket for the IPG below the clavicle and tunneling the extension (model 7495-51; Medtronic) from the scalp to the chest. Most patients left the hospital the following day (after 24 hours of treatment with antibiotic medications) although two required an additional stay because of temporary retention of urine. Patients were seen in the DBS Clinic 6 weeks later for activation of the stimulator. Patients returned to the clinic every week until the ideal stimulation parameters were found.

Assessment of Improved Functioning

Patients were assessed prospectively for any improvement in their upper-limb tremor contralateral to the thalamic stimulator. Videotapes were made preoperatively and 2 and 12 months postoperatively (once the best stimulation setting was confirmed). We used a subset of the items on the clinical rating scale of Fahn, et al.,11 for tremor. Resting tremor was assessed while patients reclined with their arms on their laps. Postural tremor was assessed with the arms held outstretched and with shoulders abducted and elbows flexed with fingers near the mouth. Action tremor was assessed during finger-to-nose testing. The videotapes were then randomized and the presence of tremor was scored by a neurologist who was blinded to the treatment. Scores were as follows: 0 = none; 1 = slight, barely perceptible, may be intermittent; 2 = moderate, amplitude less than 2 cm, may be intermittent; 3 = marked, amplitude 2 to 4 cm; 4 = severe, amplitude greater than 4 cm. An overall tremor score was calculated by summing the three individual scores.

Patients underwent a battery of tests preoperatively and 2 and 12 months postoperatively to measure prospectively any changes in their reported ability to perform selected activities and in their health-related quality of life. Patients were asked to rate their ability to perform six different ADLs (relating to hygiene, social activities, writing, dressing, feeding, and ability to work). These questions, and the patients’ possible responses, were taken from the clinical rating scale of Fahn, et al.,11 for tremor (scores: 0 = normal to 4 = most severe impairment). We selected these functional domains because the benefits of tremor reduction might be restricted to activities in which upper-limb function is important (for example, feeding, writing, and dressing).

The health-related quality of life was assessed using the SF-36. This self-reporting instrument is well validated, and yields a total score plus eight subscales that are used to assess physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health.29 Patients were encouraged to read and respond to the questions on the SF-36. In many cases, however, this was precluded by physical deficits (for example, blindness). In these cases a family member read the questionnaire to the patient and recorded their responses. Transformed subscale scores and a total score were computed using procedures described in the test manual.

Patients were also asked to complete a brief self-reporting questionnaire about their recent DBS surgery. Un-
marked questionnaires were sent to the patients’ residences between 3 and 22 months after their optimum DBS stimulation parameters were determined. At the time the questionnaire was mailed out, one of the 12 patients had died from factors unrelated to DBS implantation, reducing the sample size to 11. Self-addressed, stamped envelopes were included to facilitate anonymity and survey return. Respondents were encouraged to reply frankly to items, and they were assured that their answers would remain anonymous. Respondents were encouraged to return their completed questionnaires, which were free of identifying information, to the investigators via the mail. In an attempt to maximize survey return, a follow-up letter was sent 3 weeks after the first mailing. Completed surveys were received from nine of the 11 patients (a response rate of 82%).

Statistical Analysis

Postoperative changes in the three tremor measures and total tremor score, the SF-36 subscales and total SF-36 score, and the measures of selected ADLs were examined using paired t-tests. Because of the small sample size and resultant concerns about low statistical power, the alpha value was held at the 0.05 level for each test, and ESs (X1 - X2/pooled standard deviation) are reported for all contrasts. Small, medium, and large ESs were categorized as 0.2, 0.5, and 0.8, respectively, per the recommendation of Cohen.8 Post hoc analysis was performed using Pearson’s correlation to determine if any of the preoperative variables might have predicted a more favorable outcome. Improvements in ADL scores were correlated with preoperative tremor scores, disease duration, patient age, and education.

Results

Tremor Score

Figure 1 presents the mean resting, postural, action, and total tremor scores before and after surgery. At 2 months postoperatively, there were significant reductions in tremor as follows: 1) resting tremor was reduced to 58% of the preoperative level (ES 0.87, p = 0.02); 2) postural tremor to 57% (ES 2.78, p < 0.001); 3) action tremor to 70% (ES 2.02, p < 0.001); and 4) overall tremor to 63% (ES 3.87, p < 0.001). At 1 year, improvements were maintained in tremor as follows: 1) postural tremor remained at 56% of the preoperative level (ES 2.74, p < 0.001); 2) action tremor at 67% (ES 1.26, p = 0.005); and 3) overall tremor at 60% (ES 2.01, p < 0.001). Our sample size precluded statistical analysis of hemisphere effects. Inspection of the data from individual cases, however, indicated that the effect of surgery did not differ according to whether the DBS was targeted at the left or right thalamus.

Activities of Daily Living

Figure 2 presents the mean scores for the selected ADL items before and after surgery. The patients’ reported ability to feed themselves improved significantly after surgery (ES 0.96, p = 0.01). There was a trend toward an improvement in reported dressing ability (ES 0.58, p = 0.08). Although it was not statistically significant, there was a medium-sized improvement in personal hygiene (ES 0.45, p = 0.16), and a small improvement in reported writing ability (ES 0.3, p = 0.34). There was little postoperative change in social interaction, and no patient was able to work before or after the procedure. At 1 year, the medium-sized improvement in feeding was no longer statistically significant (ES 0.5, p = 0.17). Secondary analyses showed that lower levels of preoperative total tremor correlated with improvements in feeding (r = -0.619, p = 0.42). At 1 year, higher educational levels correlated with improvements in feeding (r = 0.667, p = 0.05) and dressing (r = 0.734, p = 0.024); short-
er disease duration correlated with improved social activities ($r = -0.767$, $p = 0.026$); and younger age correlated with improved hygiene ($r = 0.692$, $p = 0.39$).

**Health-Related Quality of Life**

There were no statistically reliable postoperative changes in the eight SF-36 subscales or in the SF-36 total score. Over the assessment period there was a medium-sized decrease in reported physical functioning (ES $0.43$, $p = 0.18$), and small-to-medium sized improvements in role-physical (ES $0.33$, $p = 0.3$), general health (ES $0.32$, $p = 0.32$), and role-emotional (ES $0.24$, $p = 0.45$). There were small to nonexistent effects on bodily pain, vitality, social functioning, and mental health.

**Satisfaction With Surgery**

Figure 3 presents the patients’ responses to the satisfaction survey. Although there was a statistically reliable improvement in tremor with DBS, the patients’ satisfaction level with the procedure was more heterogeneous. Overall, the patients were roughly evenly divided in their responses to the questions of whether, given similar circumstances, they would undergo DBS again, whether they were satisfied with the results of surgery, and whether DBS made their life better.

**Postoperative Complications**

One patient developed a wound infection of the scalp during the 2nd postoperative month and required intravenously administered antibiotic agents and explantation of the device. This patient was the most cognitively impaired preoperatively and picked at her wound postoperatively. She also experienced feeding difficulties during at the 3rd postoperative month and required a feeding tube. Her data were omitted from the results because postoperative motor, ADL, and quality of life data were unavailable. One other patient had a superficial wound infection during the 2nd postoperative month that was controlled with oral antibiotic agents and did not require explantation of the hardware. She later experienced feeding difficulty due to the progression of MS at the 6th postoperative month and died 1 month later. The most common side effect of the stimulation was transient paresthesia when the IPG was first activated. These paresthesias were not painful and usually faded after 1 minute (annoying paresthesia or any corticospinal response could be avoided by turning down the stimulation voltage). Two patients had transient postoperative urinary retention that resolved after 2 days of intermittent catheterization.

**Discussion**

There are at least 350,000 patients with MS in the United States. Neurologists can help ameliorate many symptoms attributable to this disease, but tremor and ataxia are particularly difficult to treat. Although many different movement disorders can accompany MS, tremor is the most common. Moderate or severe tremor has been estimated to occur in 32% and 6% of patients with MS, respectively. It is often difficult to correlate tremor with its causative central nervous system lesion because there are usually multiple lesions present by the time tremor occurs. Lesions in the cerebellum, its connections, and the midbrain have all been documented as causes of action tremor. Lesions of the archicerebellum usually result in a 3 to 5–Hz postural tremor of the trunk and limb girdle, whereas lesions of the neocerebellum can produce an intention tremor of the limb with various frequencies. Regardless of the cause, results of long-term follow-up studies indicate that tremor is a poor prognostic sign.

There is increasing interest in stereotactic surgery for movement disorders, including those caused by MS. In line with a repeated trend in functional neurosurgery, MS-related tremor was first treated with thalamotomy and then with thalamic DBS. Although the total number of patients with MS who are treated with this procedure is relatively small in comparison with those treated for other causes of tremor, the results are promising. Deep brain stimulation is reported to yield a lower morbidity rate compared with thalamotomy, especially in patients whose tremor involves the proximal muscles. When thalamic DBS and thalamotomy are compared for the reduction of tremor in MS, both procedures have a similar initial success rate, but DBS appears to last longer and there are fewer incidences of morbidity in the follow-up period.

There has been some confusion regarding the nomenclature of the various types of tremor found in MS. Resting tremor is not usually seen. Postural tremor, which is initiated by the continuous tonic contractions of the neck and trunk muscles, can be misinterpreted as resting tremor. Our
patients were assessed while they reclined in the sitting position with their arms resting on their laps. Even with patients in this position, resting tremor was detected and it improved after thalamic stimulation. We cannot rule out that tonic contractions of trunk musculature could have been responsible for some or all of the reported resting tremor in our patients.

Tremor in patients with MS can be assessed using any of the conventional movement disorder scales that have tremor-specific subscales. Most of these scales, however, are designed primarily for resting or postural tremors. The accompanying ataxia in patients with MS makes the clinical rating of their tremor more difficult. Other MS-related symptoms (for example, visual impairment) might negate the use of tracing spirals, maze drawings, handwriting specimens, or measurement of the volume of water spilt from a cup. In this study, we used a subset of the clinical rating scale of Fahn, et al., for tremor, which has proven reliable in patients with MS, independent of the rater. We omitted pen and paper measures of tremor from our test battery because some of our patients had visual impairment. Our measurements included resting, postural, and action tremor, as well as the sum total of all these types of tremors. This classification is somewhat arbitrary but allows for reliable scoring. We initially wanted to determine which component of the tremor was most improved by thalamic stimulation to allow us to predict which patients would benefit most during future surgeries. In this cohort, no differences were noted in the magnitude of improvements for the various tremor types. Nevertheless, patients frequently spontaneously reported that they found the reduction in action tremor to be the most important factor in terms of functional gains.

The improvements in action and postural tremor remained constant over 1 year. The magnitude of improvement was less than we usually see in our patients with essential or parkinsonian tremor. This may reflect a more widespread pathological condition in MS that is not entirely covered by the DBS. Our stimulation parameters in patients with MS typically cover a larger area (higher voltage with wider-spread contacts) than in patients with essential or parkinsonian tremor.

Improving action tremor has direct benefits for functional tasks such as feeding, dressing, writing, and personal hygiene. Although feeding was the only ADL to be significantly improved at 2 months postoperatively in our cohort, there were small to medium improvements in ES for dressing, writing, and personal hygiene. A larger sample size is needed to confirm a statistical improvement in these areas. At 1 year, there was a moderate improvement in ES for feeding, but this was not statistically significant in our cohort. Our selection criteria were deliberately kept as open as possible in an effort to determine who might derive the most benefit from this surgery. Post hoc secondary analysis indicated that patients with shorter disease duration, younger age, more education, and less severe preoperative tremor benefited more from this procedure. These patients were either less likely to develop incapacitating disease progression or may have been more able to adapt the less tremulous limb to functional activities. It was also clear in retrospect that ataxia was not improved. The patients whose ataxia was masked by severe tremor preoperatively had statistical reductions in their tremor, but their potential functional gains were blocked by the remaining ataxia.

Not all of our patients were satisfied with the procedure. Satisfaction is difficult to quantify and has many influencing factors. In the present context, it may be determined to a large extent by how closely the postoperative results match the patient’s preoperative expectations. It is important to educate patients that this procedure is for tremor only and will not improve their vision, strength, gait, bladder control, or cognition. In this way, the patients’ preoperative expectations are realistic. Our first few patients probably had unrealistic expectations that were not met, and this resulted in reduced satisfaction. With a better understanding of the results of this surgery, our patients are now better informed and are more likely to have their expectations fulfilled.

Although DBS improved tremor and selected specific ADLs that required a steady upper limb, it did not improve the patients’ overall health-related quality of life as measured by the SF-36 scale. This may reflect insensitivity on the part of the SF-36. We believe, however, that this result more likely reflects the nature and extent of the improvements in daily functioning offered by DBS to this population. Our results indicate that this procedure is effective in reducing tremor, and therefore facilitates performance of ADLs that are highly dependent on upper-limb functioning. This cohort of patients had other severe disabilities that were not targeted by surgery (for example, blindness, paraplegia, and bladder dysfunction), disabilities that appear to have worsened over the course of the study as a result of disease progression (as reflected in the decline in reported postoperative physical functioning). These severe disabilities not targeted by DBS may place limits on the overall improvement in the quality of life that may be expected with the use of DBS in this population.

Conclusions

Thalamic DBS reduces the tremor of MS and continues to be effective for at least 1 year. Reduced tremor did not always translate into improved quality of life; postoperatively, our cohort improved only in their ability to feed themselves. Trends in improved dressing, writing, and personal hygiene were seen initially but were not sustained. Although there was a consistent statistical improvement in tremor postoperatively, patient satisfaction with the procedure was variable. Patients and their caregivers need to be carefully educated preoperatively about the limited expectations of surgery (tremor reduction only), and the specific capabilities that may be enhanced by tremor reduction. Inappropriately high preoperative expectations may cause reduced satisfaction with the procedure. Further research in this field may delineate which subgroup of patients with MS who suffer from tremor will benefit most from this procedure. Restricting entry criteria to include only this subgroup would improve surgical results. Our experience indicates that younger patients with MS whose disease is of a shorter duration and who have no superimposed ataxia, weakness, or sensory loss in the tremulous limb may attain the best results.

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