Long-Term Effects of Deep Brain Stimulation for Essential Tremor with Subjective and Objective Quantification via Mailed-In Questionnaires

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Key Words

Deep brain stimulation · Essential tremor · Quality of life

Abstract

Background: Deep brain stimulation (DBS) is a standard treatment for patients with disabling essential tremor. The short-term efficacy rate is well established. **Objectives:** To assess the long-term effects of DBS in our series and evaluate the durability of the effects over time. **Methods:** Eighty-four patients implanted with unilateral or bilateral DBS for essential tremor were asked to complete three mailed-in questionnaires to assess DBS efficacy objectively and subjectively. **Results:** Twenty-six patients responded, with a median follow-up of 41 months. Approximately half of the patients had more than 48 months of follow-up. At the time of follow-up, the Tremor Rating Scale was reduced from a mean score of 7 (5–8) to 3 (2–3) with DBS OFF and ON, respectively. Quality of life, measured with a subset of items of the ADL Taxonomy, improved from a mean of 26 (23–33) to 12 (12–14), comparing DBS OFF and ON. No significant differences were seen when comparing efficacy at short- (<12 months), middle- (12–48 months) or long-term (>48 months) follow-ups. **Conclusion:** DBS has long-term efficacy for tremor control.

This is associated with sustained benefits in quality of life. The duration of the follow-up was not associated with any significant difference in efficacy.

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Introduction

Essential tremor (ET) is one of the most common movement disorders [1–3] and affects mainly the elderly population. It can lead to major functional disability, impairing the quality of life (QOL) of these patients. The treatment of medically refractory ET patients, which can occur in up to 50% of cases [4], is still considered a challenge, and that is when surgical procedures may play a role. The available surgical approaches for the treatment of this condition include ablative and modulatory techniques. Although ablative procedures are still in use in many institutions worldwide, deep brain stimulation (DBS) of the ventral intermediate nucleus of the thalamus (VIM) has become the treatment of choice for this condition. DBS is preferred over thalamotomy for its safety, adjustability and reversibility [5, 6]. The short- and middle-term outcomes of DBS for ET are well established and

have been thoroughly published [7–12]. Studies aimed at evaluating long-term effects of DBS have also been conducted, indicating a concern for loss of efficacy in a subset of patients over time [13, 14]. The total number of patients reported with long-term follow-up is still limited, and additional case series are needed to further evaluate the stability of the effects of DBS for tremor control. In this study, we evaluate the long-term results of DBS for ET utilizing three mailed-in questionnaires. The questionnaires were aimed at evaluating the extent of tremor suppression produced by DBS at the time of follow-up as well as the impact of DBS on the patients' QOL. In addition, possible prognostic factors were evaluated.

Patients and Methods

Patient Selection

Eighty-four patients underwent implantation of VIM DBS for ET (Medtronic Inc., Minneapolis, Minn., USA) between July 2000 and June 2009 at the Cleveland Clinic Department of Neurosurgery and Center for Neurological Restoration. These potential subjects were screened using the following study inclusion criteria: (1) diagnosis of ET by a neurologist; (2) DBS procedure performed only after medical therapy failure; (3) alive at time of screening; (4) competent to provide consent, and (5) did not have an additional movement disorder. Demographic data were retrospectively collected through review of the electronic and paper medical records. All patients were mailed the informed consent form and three questionnaires to be signed and completed. Patients were also contacted by phone regarding completion of the questionnaire and to address any questions. The questionnaires also included a section for objective quantification of tremor with the Archimedes Spiral and the Line-Drawing Task. The protocol was approved by the Cleveland Clinic Institutional Review Board, and all patients signed an informed consent form in order to participate in the study.

Surgical Procedure

Patients were initially selected for surgery based on significant impact on QOL, failure to respond to medical therapy and clinical suitability for surgery. After clinical evaluation with a multidisciplinary team, patients were selected for surgery and underwent either unilateral or bilateral implantation depending on tremor presentation and tremor management goals. Patients who received bilateral implants had staged procedures, with implantation of the second side performed several weeks or months after the first side.

Stereotactic implantation of the DBS leads was performed under monitored anesthesia care and/or local anesthesia. All implants were done with a Leksell G model frame (Elekta Instruments, Stockholm, Sweden). Planning and targeting of the VIM were performed in computerized planning stations utilizing volumetric magnetic resonance and/or computerized tomography images. Implantation of the DBS leads (Medtronic 3387 and 3389) was guided by microelectrode recording, microstimulation and macrostimulation with standard techniques previously described

by our group [15]. The generator(s) (Medtronic Itrel III or Soletra) was (were) placed and connected to the DBS lead in the same operation as for the lead implant or in a separate surgical procedure.

Clinical Evaluation

The three mailed-in questionnaires included items of the ADL Taxonomy [16, 17] and of the Tremor Rating Scale (TRS) [18] as well as the Archimedes Spiral and the Line-Drawing Task. The goal of the questionnaires was to evaluate the extent of efficacy of DBS compared to baseline. Since we did not have the same questionnaires completed prior to the procedure on file, the patients were asked to complete a first questionnaire based on their memory of limitations in QOL prior to the procedure. In order to reduce the bias of memory on the results of the study, we also asked the patients to complete a questionnaire to compare their QOL and activity performance at the time of the follow-up with the DBS device ON and with the DBS device OFF.

The first questionnaire addressed symptoms and QOL that patients remembered experiencing before DBS implantation, the second asked about current symptom severity and QOL with the device ON and the third asked about symptom severity and QOL with the device OFF.

The first and second questionnaires included the following items of the ADL Taxonomy: eat and drink, mobility, going to the toilet, dressing, hygiene, grooming, communication, transportation, cooking, shopping, cleaning and washing. Each item is composed of 2–6 subscales, which are rated according to the following scale, with a composite score range of 47–235: (1) performs the action independently and without difficulty; (2) performs the action independently but with some effort; (3) performs the action independently but with major effort; (4) performs the action with some help from an assistant, and (5) cannot perform the action.

In addition to these items, the questionnaires also included the drawing portion of the Fahn-Tolosa-Marin Tremor Rating Scale, which was completed by the subjects for each hand treated by DBS with the device ON and OFF. The drawings were digitally scanned, de-identified, randomly coded and sorted, and scored by a blinded neurologist with extensive expertise in scoring the test. Each drawing component had a score of 0–4, with a possible composite score range of 0–12 for each hand. Higher scores indicate more severe tremor. Several drawings were duplicated and scored with the others for evaluation of intrarater reliability.

The third questionnaire was a simplified version of the previous two questionnaires. The patients were asked to complete the third questionnaire in bed with a supervisor to control for safety issues. The patients were asked to turn the pulse generator(s) OFF at night and to complete the questionnaire in the morning prior to turning the devices back ON. The questionnaire was simplified in order to reduce the burden to the patient and allow for quickly turning the devices back ON. It included three items of the ADL Taxonomy (eat and drink, dressing and communication), each composed of 3–5 subscales (which should be rated according to the same scale described previously) and with a composite score range of 12–60. The drawing portion for the objective tremor evaluation was the same used on the other questionnaires.

Statistical Analysis

The results of the point estimates are reported as medians with interquartile ranges (IQR), 95% confidence intervals (CI) or frequencies with percentages where applicable. All composite scores

for tremor or QOL were treated as continuous variables. For paired scores (within an individual), the Wilcoxon signed-rank test was used to test the null hypothesis of no score difference. Unpaired scores were compared using the Wilcoxon rank-sum test. CI for median scores were calculated using the percentile method on 10,000 bootstrap samples. All statistical tests were performed using JMP version 8 (SAS Institute, Inc.) and SAS version 9.2 (SAS Institute, Inc.). We set a threshold of significance at $\alpha \leq 0.05$ and did not correct for multiple comparisons, except where indicated.

Results

Characteristics of Study Participants

We sent surveys to 84 patients who could be identified based on records to meet the inclusion criteria for our study. We received surveys back from 26 (31%) eligible subjects, from which 15 (58%) were male. To the extent possible, non-responders were classified by reason for not participating: 6 (11%) were deceased, 6 (11%) were not interested in participating, 33 (58%) were unreachable, 4 (7%) failed inclusion criteria due to other concurrent neurological diagnosis at the time of the follow-up and 9 (16%) were not included because their questionnaires were incomplete or because the patients failed to follow instructions in filling out the questionnaire and drawing spirals. Tables 1 and 2 summarize the demographics of the subjects included.

Objective Quantification of Tremor Scores with DBS ON and OFF

Tremor severity was determined by interpretation of the drawing portion of the Fahn-Tolosa-Marin score. There was an intrarater composite score correlation coefficient of determination (R^2 value) of 0.86. There were 26 independent observations from left-sided procedures available to calculate medians and CI.

The median score with the device OFF was 7 (95% CI: 5–8), and the median score with the device ON was 3 (95% CI: 2–3). The median composite difference in tremor score comparing ON and OFF was 4.0 points (95% CI: 3–5; $p < 0.0001$). None of the covariates tested (age, gender, time since surgery, disease duration or bilateral implant) had any significant effect on tremor scoring with DBS OFF or ON.

Presurgical QOL versus Current QOL with DBS ON

Patients were given a modified version of the QOL instrument to be completed regarding QOL prior to surgery (as recollected) and at the time of follow-up with DBS

Table 1. Characteristics of study participants (n = 26)

	At time of first surgery	Current
Age, years	68 (58–77)	72 (62–82)
Male gender, n (%)	15 (58)	15 (58)
Disease duration, years (n = 22)	32.5 (19–48)	35.5 (20–51)
Side operated on		
Left only	23	17
Right only	3	0
Both sides		9

Values are median (IQR) or n (%), unless otherwise indicated.

Table 2. Participants per follow-up period

	Number of patients (%)
<12 months	6 (23)
13–24 months	2 (8)
25–48 months	6 (23)
>48 months	12 (46)

ON. The questionnaire had 12 subscales. One subscale, ‘transportation’, was removed from the analysis due to low response rates. The score ranged from 42 to 210, with higher scores indicating worse QOL. Twelve composite measurements were excluded due to missing data. The remaining measurements were grouped by subject to make them non-redundant. The final composite analysis was carried out on 20 subjects.

The median score for preoperative QOL was 85 (95% CI: 68.5–94), and the median score for postoperative QOL with DBS ON was 47.5 (95% CI: 46.5–49). The median difference in the total scores between preoperative and postoperative QOL with DBS ON was 33 (95% CI: 21–42), which was statistically significant. None of the variables studied (age, gender, bilateral implantation, disease duration or time since surgery) were significantly correlated with outcome.

When individual subscales were tested, including all patients with complete data, a significant improvement in QOL was seen for each scale comparing preoperative to postoperative DBS ON. These data are summarized in table 3.

We also analyzed the distribution of subjects who experienced an improvement in their QOL by at least 15 points, which we deemed to be a clinically significant im-

Fig. 1. Study outcome variables comparing current tremor score with DBS ON or OFF (left), presurgical QOL and current QOL with DBS ON (middle) and current QOL with DBS ON or OFF (right). Values are displayed as means, with error bars representing IQR. All changes were statistically significant.

provement in QOL. Of the 20 subjects with sufficient data, 16 (80%; 95% CI: 58–91) showed a clinically significant improvement. No patients reported a decrease in QOL.

QOL with DBS ON Compared to DBS OFF at the Time of Follow-Up

Patients were given a modified version of the QOL instrument and were asked to complete it with the DBS ON or OFF. Twenty non-redundant subjects were evaluated for difference between current QOL with DBS ON and OFF on a subset of the total questionnaire, evaluating the subscales ‘eat and drink’, ‘dressing’, and ‘communication’. The possible score range was 12–60, with higher scores indicating worse QOL.

The median scores with the DBS OFF and DBS ON were 31 (95% CI: 24–38) and 12 (95% CI: 12–14), respectively. The median difference in the total scores was 15.5 (95% CI: 11–23.5). None of the variables studied was correlated with DBS outcome, including time of follow-up.

Presurgical QOL versus Current QOL with DBS OFF

With the intent to recognize possible disease progression, we also compared the median scores of subsets of the preoperative QOL questionnaire with the comparable data from the questionnaire of current QOL with DBS OFF. The results were 26.5 (95% CI: 23–33.5) and 31 (95% CI: 24–38.5), respectively. Although there was a trend for

Table 3. Mean improvement in QOL subscale scores from before DBS surgery versus currently with DBS ON

Subscale	Mean improvement	p value
Eating/drinking (n = 20)	5.55	<0.0001
Mobility (n = 18)	1.5	0.002
Toileting (n = 20)	1.2	0.02
Dressing (n = 20)	3	0.0002
Hygiene (n = 20)	1.6	0.004
Grooming (n = 16)	6.5	<0.0001
Communication (n = 20)	3.9	<0.0001
Transportation (n = 13)	2	0.02
Cooking (n = 19)	3.9	0.0001
Shopping (n = 19)	1.9	0.0005
Cleaning (n = 19)	1.2	0.0005
Washing (n = 18)	1.1	0.02

p values were calculated from Wilcoxon signed-rank tests.

worsening scores (–4; 95% CI: –8.5 to –3), the difference was not significant. The data for QOL acquired with all questionnaires is summarized in table 4.

Figure 1 summarizes the study data, including the effects of DBS on tremor evaluated objectively with the drawing portion of the TRS at the time of follow-up as well as QOL as remembered by the patient (first and sec-

Table 4. Comparisons of median tremor scores with DBS ON and OFF at the time of follow-up, comparison of QOL scores with DBS ON and OFF at the time of follow-up (subset) as well as comparison of presurgical QOL and current QOL with DBS ON (full)

	Presurgical	Current, DBS OFF	Current, DBS ON	Difference
Tremor score		7 (5–8)	3 (2–3)	4* (3–5)
QOL (subset)	26.5 (23–33.5)	31 (24–38.5)	12 (12–14)	15.5* (11–23.5)
QOL (full)	85 (68.5–94)		47.5 (46.5–49)	33* (21–42)

All values are scores with 95% CI. Difference values represent the median difference for paired observations.

* Statistically significant difference.

Table 5. Effects of DBS on tremor control and QOL per follow-up period

	Total sample	<12 months	12–48 months	>48 months
Difference in tremor score (DBS OFF – DBS ON)	4 (3–5)	5 (2.5–6.5)	3 (2.5–6.5)	5 (0–8)
Difference in QOL (subset) (DBS OFF – DBS ON)	15.5 (11–23.5)	13 (4–23)	17 (11–26)	18 (11–31)
Difference in QOL (full) (preoperative – DBS ON)	33 (21–42)	22 (3–45)	35 (24–41)	36 (20–70)

ond questionnaires) and subscores of QOL measured at the time of follow-up with DBS ON and OFF (third questionnaire).

Tremor Control and QOL Outcome per Follow-Up Period

Our statistical analysis showed no significant effect of the duration of follow-up on the effectiveness of DBS for tremor control and QOL. Nevertheless, given prior reports suggesting a higher risk for loss of efficacy over time, we compared the rate of efficacy of DBS on objective tremor control and QOL measures (full and subset) for each of the following follow-up periods: <12, 12–48 and >48 months. There was no significant difference in tremor control or QOL comparing short- and long-term follow-up. Patients with less than 12 months of follow-up had a non-significant trend for less QOL improvement for the same level of tremor control. The data are summarized in table 5.

Discussion

QOL is significantly impaired in a great proportion of ET patients [19]. This functional disability is due not only to the physical limitations the tremor itself induces but also to the social embarrassment and withdrawal these

patients suffer. The safety and efficacy of stimulation of the VIM are well documented in the literature [20–23] and, although thalamotomy and DBS may provide comparable improvement of the condition, adverse effects (such as dysarthria, cognitive deterioration and gait disturbances) are generally more common with ablative procedures [24]. Our data corroborates that VIM DBS improves tremor and performance in a variety of daily living even several years after implantation. This was evaluated subjectively, asking patients to report on how they remembered QOL to be prior to implantation as well as objectively. The patients were asked to complete the drawing portion of the TRS with DBS ON and OFF and to complete a questionnaire about simple QOL measures having the DBS system ON and OFF. Since most patients keep the systems ON, we wanted patients to re-evaluate their symptoms and limitations with the DBS systems OFF at the time of follow-up so that a proper comparison could be drawn to the effects of DBS at the time of follow-up.

One of the most common variables used for evaluating outcomes after surgical procedures for ET is improvement in tremor severity. Zhang et al. [23] showed a significant decrease in the TRS (approx. 80% of improvement) in both handwriting and tremor components after an average of 56.9 months. The same was observed by Pahwa et al. [9], who described a 75% improvement with

unilaterally implanted DBS, and by Koller et al. [13], who reported a 78% improvement in the contralateral arm after unilateral implants after 40 months of follow-up. Our analysis is in accordance with the literature and, after a mean follow-up of 41 months, there was a 57% improvement in tremor scores with the DBS device ON compared to the DBS device OFF.

QOL is another variable addressed to infer outcomes after surgical procedures for ET. According to Lyons et al. [25], all their 22 ET patients assessed after a mean post-operative follow-up of 11 months referred improvement in daily functioning (with stimulation on compared to stimulation off). Moreover, the patients' rating was consistent with the clinicians' assessment (58 vs. 54%, respectively). Bryant et al. [26] also demonstrated an improvement of 44% in ADLs with DBS. However, after an average follow-up of 13 months, 4 of 16 patients did not sustain improvement and would not have the procedure repeated, pointing out the fact that patient satisfaction was directly proportional to improvement in daily activities and tremor control and that loss of efficacy could occur in ET patients after VIM DBS. Patients who initially responded well to DBS with good tremor control and later lost efficacy have been reported [13, 14] and can be challenging to manage. Options include reprogramming the DBS device as well as revising the lead or adding additional leads in novel targets [27–29]. In the present series, we attempted to evaluate the efficacy of DBS according to follow-up time. Although the patients were not followed prospectively, the methods allowed for subjective as well as objective evaluation of tremor severity and QOL in patients implanted over a long period of time (approximately half of the patients included were followed for more than 4 years). The rate of tremor control scored on the drawing portion of the TRS was similar in patients followed for 12–48 months compared to those followed for more than 48 months. Similar findings were observed for QOL with the full or abbreviated questionnaires. Interestingly, patients with short-term follow-up (<12 months) seemed to report less improvements in QOL for similar (or slightly greater) improvements in tremor control. Although the methods utilized do not allow us to exclude the possibility that a few patients lost some tremor control over time, the results point to a long-term stability of the effects of thalamic DBS for tremor control.

Study limitations and caveats include the low number of patients who contributed to the final data set and the general methodology of the study, which relies only on mailed-in questionnaires without face-to-face evaluation. A significant number of patients were lost to follow-

up, which may also have biased the result. Not all the patients completed the entire questionnaire as requested, and one of the questionnaires was completed according to the memory and expectations of the patients, which could also have biased the results. Nevertheless, we obtained the same result with a comparison of functionality during ON and OFF stimulation at the time of follow-up, which did not rely on memory. Tremor rebound could be a concern as patients were asked to perform ADLs and draw spirals with the device OFF. The rebound effect could theoretically magnify the DBS OFF tremor and bias the impression of efficacy. This concern should be minimized because the spirals were drawn in the morning, after the device had been OFF overnight. Hence, only rebound effects that lasted more than 6–8 h could have affected the outcomes. Moreover, the rating of the Archimedes Spirals drawn with DBS OFF and ON was blinded and objective. This points to the validity of the findings even though we did not have a QOL questionnaire completed preoperatively on file. The punctual evaluation also limited the interpretation of individual long-term results and may not account for disease progression. Nevertheless, the data of this study, comparing QOL as remembered preoperatively to QOL as rated currently (with DBS OFF), do not point to a significant progression of disease during the follow-up period.

The present study corroborates that VIM DBS is efficacious for tremor in the short as well as the long term. There was no significant change in tremor control or QOL improvement comparing patients with shorter or longer follow-up periods, indicating that the benefits are long-lasting.

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