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Tremor and Other Hyperkinetic Movements

Brief Reports

Comparison of VIM and STN DBS for Parkinsonian Resting and Postural/Action Tremor

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Abstract

Background: Resting tremor is common in Parkinson's disease (PD), but up to 47% of PD patients have action tremor, which is sometimes resistant to medications. Deep brain stimulation (DBS) of the ventral intermediate nucleus (VIM) of the thalamus or subthalamic nucleus (STN) is effective for medication-refractory tremor in PD, though it remains unclear whether STN DBS is as effective as VIM DBS for postural/action tremor related to PD.

Methods: We carried out a single-center retrospective review of patients with medication-refractory resting, postural, and action PD tremor, treated with either VIM or STN DBS between August 2004 and March 2014. We assessed the degree of improvement using items 20 and 21 of the Unified Parkinson's Disease Rating Scale (UPDRS) motor scale and examined the proportion of patients achieving tremor arrest.

Results: A total of 18 patients were analyzed, 10 treated with STN and eight treated with VIM, with similar off-medication motor UPDRS scores. There was no significant difference in improvement in tremor scores or in the proportion of patients experiencing tremor arrest between the two stimulation sites. Overall, 56% and 72% of patients experienced complete absence of postural/action tremor and resting tremor, respectively, at last follow-up.

Discussion: This study demonstrated excellent outcomes on both resting and postural/action tremor after either VIM or STN DBS. Resting tremor improved to a greater degree than postural/action tremor in both groups. These results suggest that a large randomized controlled trial is needed to show a superior effect of one target on PD tremor.

Keywords: Action tremor, Parkinson's disease, deep brain stimulation

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Introduction

Although resting tremor is one of the most characteristic features of Parkinson's disease (PD), as many as 47%[1] of PD patients have action tremor, which is likely to be intrusive in daily tasks. Some patients with resting tremor exhibit only mild and non-progressive bradykinesia, rigidity, or gait disturbance. This syndrome is recognized as tremor-predominant parkinsonism or benign tremulous parkinsonism (BTP) and includes resting tremor and, in many cases, moderate to marked postural tremor.[2] Similar to the resting tremor of typical PD, action tremor in PD may also be resistant to medications, including levodopa.[2,3]

Deep brain stimulation (DBS) of the ventral intermediate nucleus (VIM) of the thalamus is an effective treatment for medication-refractory tremor in both essential tremor (ET) and PD[4–6] but does not improve other parkinsonian features. In contrast, subthalamic nucleus (STN) DBS improves tremor, as well as bradykinesia, rigidity, and levodopa-related motor complications.[7,8] In patients with severe, medication-refractory PD tremor, the degree of benefit for the resting, postural, and action components of tremor are relevant when deciding which structure should be targeted. Only a few studies have examined the efficacy of these two targets for treatment of tremor while none of these has compared the response of resting and postural/action tremor to DBS at the two sites.[3,9,10]

We carried out a retrospective review of patients in our center with BTP who had medication-refractory postural and action tremors that

were treated with either VIM or STN DBS and assessed the degree of improvement with respect to each of these action tremor types.

Methods

This is an institutional review board-approved retrospective review of 21 patients with medication-refractory PD-related tremor who were treated at the Beth Israel Deaconess Medical Center with either VIM or STN DBS between August 2004 and March 2014. All patients met Queen Square Brain Bank Criteria for idiopathic PD.[11] Criteria for study inclusion included 1) the presence of both resting and postural tremor with an action component >1 on items 20 and 21 of the Unified Parkinson's Disease Rating Scale (UPDRS) motor scale; 2) at least one other cardinal feature of PD such as bradykinesia or rigidity; 3) lack of improvement in tremor despite multiple medication trials, including dopamine agonists and levodopa. Patients with pure resting tremor without an action component were excluded from this analysis. The presence of motor fluctuations and/or dyskinesias was not an exclusion criterion.

Details of the surgical procedure were described in a previous publication.[12] Proper lead localization was confirmed post-operatively using either computerized tomography or magnetic resonance imaging. Stimulation therapy was initiated 2–4 weeks after implantation of the electrodes. During the first 3 post-operative months, stimulation parameters were adjusted to achieve optimal control of tremor without side effects. Follow-up was performed at routinely scheduled visits, usually every 3–6 months, unless the patient reported an urgent complication or other issue. Clinical efficacy, stimulation parameters, and impedance analyses were recorded at each follow-up visit.

The charts of 21 patients were reviewed. Of these, we identified 18 patients who fulfilled the inclusion criteria. Two patients were excluded because their tremor had only a rest or postural component. One patient who required VIM and STN DBS to improve severe tremor was also excluded. Tremor severity was evaluated using items 20 (rest tremor) and 21 (action or postural tremor) of the UPDRS motor scale (UPDRS III) for the contralateral hand. Each item ranges from 0 to 4, with a larger score signifying more severe symptoms. Tremor scores were recorded at baseline, after initial DBS programming, and at the most recent follow-up visit. The Wilcoxon rank sum test was employed to determine the statistical significance of differences in the postural and action tremor (item 21) scores before and after DBS and to compare the tremor score improvements achieved with each of the two targets. A p value of 0.05 was considered to be statistically significant.

Results

Of the 18 patients who were included in the study, the mean age at tremor onset was 54.8 years (SD 11.9, range 37–74 years) (Table 1). Ten patients underwent STN DBS and eight patients underwent VIM DBS. Each of the leads was implanted in the hemisphere contralateral to the most affected side except for two patients who had staged bilateral STN lead implants. Only the limb tremor contralateral to the first side implanted was included for analysis to eliminate any question of ipsilateral benefit. The two groups were similar in terms of age at tremor onset, disease duration, and motor impairment as assessed by the UPDRS III. The mean time from tremor onset to DBS surgery was 10.5 years for the VIM group (range 5–27 years) vs. 9.8 years for the STN group (range 3–32 years). Two patients had prolonged tremor duration of 27 and 32 years, and were thought possibly to have had ET preceding the onset of PD. The mean UPDRS III score in the off-medication state was 29.2 and was not significantly different between the two groups (VIM 30.6 vs. STN 28.2, $p = 0.81$). Only two of the subjects had peak-dose dyskinesias and wearing off.

There was no significant difference in the degree of improvement in postural/action tremor scores generated by VIM thalamic vs. STN DBS. Postural or action tremor (UPDRS item 21) improved 72% in the VIM DBS group vs. 68% in the STN group ($p = 0.97$). Patients who received VIM thalamic DBS started with a mean baseline postural/action tremor score (item 21) of 3.3 (SD 1.0, range 2–4), which improved to 0.8 (SD 0.9, range 0–2). Patients receiving STN DBS started from a mean baseline postural/action tremor score of 1.9 (SD 1.0, range 1–4) improving to 0.4 (SD 0.5, range 0–1). Of the nine patients with a baseline postural/action tremor score of 3 or greater, three received STN stimulation while six received VIM stimulation. Each of these three had post-surgical tremor scores of zero at last follow-up (range 24–60 months). Following programming, 10 of the 18 patients had complete absence of tremor. This represents 50% (four of eight) of the patients treated with VIM DBS and 60% (six of 10) of patients receiving STN DBS. In three subjects, neither postural nor action tremor improved after programming (two STN, one VIM), but these patients did demonstrate improved resting tremor, which had been of greater severity.

There was a 91% improvement in rest tremor (UPDRS III item 20) in the VIM group and an 89% improvement in the STN group ($p = 0.91$). The baseline preoperative rest tremor scores were 3.1 (SD 1.4) and 2.9 (SD 0.8) respectively, improving to 0.4 (SD 0.7) and 0.3 (SD 0.5) respectively. Thirteen of the 18 patients had complete absence of rest tremor, scoring zero on item 20. This represented 75% (six of eight) of the VIM group 70% (seven of 10) of the STN group.

We assessed whether there was any worsening of tremor comparing the first post-programming visit to the most recent follow-up visit. The mean postural/action tremor score increased slightly in the VIM group from the first post-programming score to the most recent follow-up visit based on three individuals who had worsened by at least a point. There was only one individual in the STN group who had worsening of postural/action tremor score and the difference in the change scores did not reach statistical significance ($p = 0.45$). In contrast, the mean resting tremor score remained unchanged from post-programming to most recent follow-up in both the STN and VIM groups. The mean time to last follow-up was 40 months (range 1–108 months with slightly longer follow up in the VIM group (mean 48 months) vs. the STN group (mean 35 months). In addition, there were no statistically significant differences in stimulation parameters assessed at last follow-up (Table 1). Finally, adverse events in the two groups were examined. Adverse events included post-operative

Table 1. **Comparison of Clinical Characteristics, Tremor Severity, and Programming Parameters by Target**

	VIM (n=8)	STN (n=10)
M:F	7:1	8:2
Age at onset (mean, SD), years	54.7 ± 11.9	53.6 ± 13.3
Disease duration (mean, SD), years	10.5 ± 7.5	9.8 ± 9.1
Total off medication motor UPDRS score (mean, SD)	30.6 ± 12.3	28.2 ± 14.6
Baseline postural/action score		
Severe, 4	5	1
Moderately severe, 3	0	2
Moderate, 2	3	3
Mild, 1	0	4
Pre-surgery item 21 score (mean, SD)	3.3 ± 1.0	1.9 ± 1.0
Post-programming item 21 score (mean, SD)	0.8 ± 0.9	0.4 ± 0.5
Rationale for target selection		
Chief complaint action tremor	8	
Chief complaint resting tremor		1
Bothersome levodopa-responsive bradykinesia/rigidity		4
Prior thalamotomy		1
Younger age (age <60)		2
Motor complications		2
Percentage improvement (mean, SD)	71.9 ± 36.4	68.1 ± 44.1
Complete postural/action tremor suppression, number of patients (%)	4 (50%)	6 (60%)
Long-term post-surgery item 21 score (mean, SD)	1.0 ± 0.8	0.3 ± 0.5
Pre-surgery item 20 score (mean, SD)	3.1 ± 1.4	2.9 ± 0.8
Post-programming item 20 score (mean, SD)	0.4 +/_0.7	0.3 ± 0.5
Percentage improvement (mean, SD)	90.6 ± 18.6	88.9 ± 20.5
Complete rest tremor suppression, number of patients (%)	6 (75%)	7 (70%)
Long-term post-surgery item 20 score (mean, SD)	0.4 ± 0.7	0.2 ± 0.4
Length of follow-up (months, mean, SD)	48.0 ± 41.0	34.9 ± 24.0

Table 1. Continued

	VIM (n=8)	STN (n=10)
Monopolar vs. bipolar stimulation, Number of leads (n=20)	6:2	9:3
Voltage (mean, SD)	3.3 V ± 0.9	3.1 V ± 0.7
Pulse width (mean, SD)	98 μs ± 41.7	75 μs ± 23.9
Frequency (mean, SE)	164 Hz ± 27.2	163 Hz ± 28.9

F, Female; M, Male; SD, Standard Deviation; SE, Standard Error; STN, Subthalamic Nucleus; UPDRS, Unified Parkinson's Disease Rating Scale; VIM, Ventral Intermediate Nucleus.

encephalopathy (one STN), worsening of gait (one STN), and functional lower extremity weakness with DVT (one VIM).

Discussion

We compared the long-term improvement of resting with postural/action tremor after VIM and STN DBS surgery. We found a consistent improvement in both resting and postural/action tremor with either VIM thalamic or STN stimulation, with 10 of the 18 (56%) patients experiencing complete absence of postural/action tremor and 72% experiencing complete absence of resting tremor at last follow-up. There was no significant difference between the two stimulation sites regarding both mean tremor improvement and the proportion of patients experiencing complete tremor control.

A prior study by Savica et al.[3] demonstrated either complete resolution or reduction in resting tremor in 87% of subjects receiving either STN or thalamic stimulation. Action tremor was not assessed. Two previous studies examined the impact of STN DBS on action tremor, demonstrating improvements 1–2 years after surgery.[9,10] Longer-term benefit was not examined. Studies examining the long-term effects of DBS have mainly shown a benefit in resting tremor.[5,6] In this analysis, we were able to demonstrate improvement in action tremor with stimulation at either the VIM or STN, both after surgery and at last follow-up, which occurred at a mean of 40 months. These findings raise the possibility that either target may be reasonably equivalent in treating parkinsonian postural/action tremor. In this scenario the clinical decision-making regarding target selection may need to focus on consideration of adverse effects, the possibility of benefit on other features such as bradykinesia, rigidity, or dystonia, or duration of benefit. In this study we were not able to detect any difference in complication rates although we did not examine impact on cognition, which may be the most fruitful area for study given concerns about cognitive impairment after STN DBS.[12]

With respect to duration of benefit, we did observe increasing mean tremor scores over time in three individuals in the VIM thalamic DBS group; this was present in one subject in the STN DBS group. Worsening tremor in the VIM thalamic DBS group is of interest in view of the progressive decline in benefit demonstrated in patients with ET.[13] It should be noted, however, that tremor was worse at baseline within the VIM group and the length of follow-up in the VIM thalamic DBS group was longer (48 months) than the STN DBS group (35 months). Both of these factors may have biased the VIM DBS group towards higher tremor scores at last follow-up. The difference in long-term follow-up duration also likely reflects changes in clinical practice with greater use of the VIM target earlier and a transition to the STN target after its approval in 2002. In addition, our data suggest that target preference tended towards VIM implantation in patients with more severe baseline tremor even after Food and Drug Administration approval of the STN target for PD. In this study, VIM stimulation parameters were slightly higher than STN stimulation parameters, which may reflect the fact that unilateral VIM stimulation may allow for higher stimulation parameters to be used in severe tremor without incurring unacceptable side effects. An alternative explanation is that greater stimulation is required to achieve a satisfactory effect in VIM DBS for severe parkinsonian postural/action tremor.

The specific neuroanatomic networks subserving action tremor and resting tremor has been the subject of much debate and speculation. The cerebellothalamocortical network is likely to be implicated in most types of tremor, including resting tremor and action tremor,[14] which would suggest that VIM DBS would be beneficial for both types of tremor. In particular, the postural tremor in PD may actually be a form of re-emergent rest tremor, reappearing only when no other motor demands are placed on the limb.[15] However, whether parkinsonian action tremor differs from other types of action tremor, as in ET, remains unclear. Additionally, evidence that both VIM and STN networks overlap at the motor cortex and that DBS at either site may interrupt tremor signals transmitted through the motor cortex[16] suggests that both may be equally efficacious because of effects on the final common pathway.

This study has several limitations that may impact our conclusions. Firstly, this was a retrospective study with limited power to detect a meaningful difference in the percentage of patients experiencing tremor suppression following either STN or VIM DBS for both resting and postural/action components for parkinsonian tremor. We conclude that DBS at both targets was effective in reducing, or resolving the action component of parkinsonian tremor, in the short

and long term. Secondly, a formalized tremor rating scale was not used to assess action tremor, but, instead, items 20 and 21 of the UPDRS III were used to measure both postural and action tremor severity.

In conclusion, we found excellent outcomes on both resting and postural/action tremor after both VIM thalamic and STN DBS in patients with medication-refractory action tremor. A high proportion in both groups achieved post-programming and long-term follow-up resting and postural/action tremor scores of zero with stimulation. Based on the data showing similar efficacy in this study, prospective studies with a very large sample size and randomized target selection would be necessary to determine the comparative efficacy and durability of VIM thalamic versus STN DBS stimulation in improving tremor in patients with combined resting and action tremor associated with PD.

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