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Randomized Trial of Focused Ultrasound Subthalamotomy for Parkinson's Disease

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ABSTRACT

BACKGROUND

The subthalamic nucleus is the preferred neurosurgical target for deep-brain stimulation to treat cardinal motor features of Parkinson's disease. Focused ultrasound is an imaging-guided method for creating therapeutic lesions in deep-brain structures, including the subthalamic nucleus.

METHODS

We randomly assigned, in a 2:1 ratio, patients with markedly asymmetric Parkinson's disease who had motor signs not fully controlled by medication or who were ineligible for deep-brain stimulation surgery to undergo focused ultrasound subthalamotomy on the side opposite their main motor signs or a sham procedure. The primary efficacy outcome was the between-group difference in the change from baseline to 4 months in the Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor score (i.e., part III) for the more affected body side (range, 0 to 44, with higher scores indicating worse parkinsonism) in the off-medication state. The primary safety outcome (procedure-related complications) was assessed at 4 months.

RESULTS

Among 40 enrolled patients, 27 were assigned to focused ultrasound subthalamotomy (active treatment) and 13 to the sham procedure (control). The mean MDS-UPDRS III score for the more affected side decreased from 19.9 at baseline to 9.9 at 4 months in the active-treatment group (least-squares mean difference, 9.8 points; 95% confidence interval [CI], 8.6 to 11.1) and from 18.7 to 17.1 in the control group (least-squares mean difference, 1.7 points; 95% CI, 0.0 to 3.5); the between-group difference was 8.1 points (95% CI, 6.0 to 10.3; P<0.001). Adverse events in the active-treatment group were dyskinesia in the off-medication state in 6 patients and in the on-medication state in 6, which persisted in 3 and 1, respectively, at 4 months; weakness on the treated side in 5 patients, which persisted in 2 at 4 months; speech disturbance in 15 patients, which persisted in 3 at 4 months; facial weakness in 3 patients, which persisted in 1 at 4 months; and gait disturbance in 13 patients, which persisted in 2 at 4 months. In 6 patients in the active-treatment group, some of these deficits were present at 12 months.

CONCLUSIONS

Focused ultrasound subthalamotomy in one hemisphere improved motor features of Parkinson's disease in selected patients with asymmetric signs. Adverse events included speech and gait disturbances, weakness on the treated side, and dyskinesia. (Funded by Insightec and others; ClinicalTrials.gov number, NCT03454425.)

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A Quick Take is available at NEJM.org

Parkinson's disease is characterized by bradykinesia, rigidity, and resting tremor.[1] Several medical treatments are available, but refractory motor manifestations such as tremor and motor complications impair quality of life for many patients.[2] Deep-brain stimulation of the subthalamic nucleus has become the preferred neurosurgical approach in place of ablative procedures such as pallidotomy and thalamotomy.[3,4] Magnetic resonance–guided focused ultrasound allows for the ablation of deep-brain structures, including the subthalamic nucleus, without craniotomy and electrode penetration and is being investigated as a treatment for Parkinson's disease.

Focused ultrasound thalamotomy has been approved by the Food and Drug Administration to treat essential and parkinsonian tremors.[5,6] Results from two uncontrolled studies have suggested that focused ultrasound subthalamotomy and pallidotomy performed on one side may reduce motor manifestations of Parkinson's disease.[7,8] Patients are potential candidates for ultrasound ablation if they have prominently asymmetric parkinsonism, if they are not considered to be clinically suitable candidates for surgery because of contraindications, or if they are reluctant to undergo a brain operation or to have an implanted device. We conducted a prospective, randomized, sham-controlled, double-blind trial of focused ultrasound subthalamotomy, performed on one side, for the treatment of Parkinson's disease in a selected group of patients with highly asymmetric motor signs.

METHODS

PATIENTS

In this trial, we considered for enrollment patients who had received a diagnosis of Parkinson's disease according to the U.K. Brain Bank Clinical Criteria[9] at the Centro Integral de Neurociencias AC (CINAC), University Hospital HM Puerta del Sur, in Mostoles, Spain, and at the University of Virginia Medical Center. Patients were included in the trial if they had highly asymmetric parkinsonism (asymmetry index, >1.5) at a screening visit; the asymmetry index is the ratio of the motor score on the Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS, part III) for the more affected side of the body to the score on the less affected side, with an index of 1 indicating symmetric parkinsonism.[7,10] The patients' motor signs were not well controlled on the more affected side despite the use of dopaminergic medication according to the treatment recommendations of the European Federation of Neurological Societies and the Movement Disorder Society–European Section[11] and as determined by four of the investigators. Therapeutic alternatives to participation in the trial, including the continuation of medication or the use of deep-brain stimulation in one or both hemispheres, were described in detail to potential enrollees before consent was obtained. All the patients provided written informed consent for trial participation. Patients chose to participate in this trial of ultrasound subthalamotomy because they declined to undergo deep-brain stimulation (11 patients); had minor motor signs on the less affected side, no meaningful levodopa-related motor complications that would make the patient a candidate for deep-brain stimulation, or both (26 patients); or were poor candidates for intracranial surgery owing to advanced age or coexisting conditions (3 patients).

The main exclusion criteria were axial motor manifestations of Parkinson's disease or motor signs on both sides of the body that were too severe (defined as a score of ≥2.5 on the modified Hoehn and Yahr scale[12] while the patients were in the on-medication state; scores range from 1 [involvement on one side only] to 5 [confinement to bed or wheelchair], with a score of 2.5 indicating mild disease with involvement on both sides and with recovery on the pull test, in which the examiner pulls the patient's shoulders from behind to induce postural instability); severe levodopa-induced dyskinesia; a history of stereotactic surgery or brain hemorrhage; the presence of cognitive impairment or any another serious neuropsychiatric or medical condition; claustrophobia that prevented the patient from undergoing magnetic resonance imaging (MRI); and a skull density ratio (an index of ultrasound penetration in the skull) of less than 0.35.[13] The complete inclusion and exclusion criteria are provided in the Supplementary Appendix, which is available with the full text of this article at NEJM.org.

TRIAL DESIGN AND OVERSIGHT

This randomized, controlled, double-blind trial compared focused ultrasound subthalamotomy with a sham procedure (sham delivery of ultra-

sound acoustic energy); medical therapy was used in both groups. Randomization in a 2:1 ratio of focused ultrasound subthalamotomy to the sham procedure was performed with the use of a Microsoft Excel random-number-generator function. Each trial-group assignment was sealed in a numbered envelope; assignments were separated into four blocks of 10 to ensure the equal distribution of sham procedures.

The trial conformed to the principles of the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the ethics committee at each participating center. The first and last authors designed the trial protocol (available at NEJM.org) and supervised the trial. One of the trial sponsors, Insightec, manufactured and contributed the ultrasound device, maintained the electronic database of the patients' characteristics and outcomes, arranged for an independent data and safety monitoring board, contracted for the statistical analysis by an independent biostatistics company (TechnoStat), and provided financial support for the trial. Insightec and the other (noncommercial) sponsors did not have any role in the trial design, in other aspects of data analysis or interpretation, or in the preparation of the manuscript, except that Fundación Hospitales de Madrid provided funds for assistance with copy editing of an earlier version of the manuscript. There were confidentiality agreements between Insightec and the authors. The first author and the last two authors wrote the first draft of the manuscript and made the decision to submit the manuscript for publication. All the authors vouch for the accuracy and completeness of the data, for the complete reporting of adverse events, and for the adherence of the trial to the protocol (including the statistical analysis plan).

TRIAL PROCEDURES

Patients were placed in the MRI equipment and were coupled to the ultrasound transducer through a stereotactic head frame. All the patients underwent identical preparation procedures, and the trial-group assignment was revealed to the trial team immediately before the procedure was started. Acoustic energy delivered by each sonication was monitored in real time by magnetic resonance thermometry and was adjusted to reach ablative temperatures of greater than 54°C in patients who had been assigned to the active-treatment group, whereas the power was disengaged for sham procedures. All the other actions of the trial team were identical in the two groups.

During the procedure, patients provided verbal feedback about subjective adverse events, such as nausea or head pain, and about motor-symptom relief. The investigators assessed the cardinal motor features (tremor, rigidity, and bradykinesia) on the more affected side of the body and observed for side effects including pyramidal signs, limb dysmetria, and speech abnormalities. In the active-treatment group, adjustment of the acoustic energy power and the collection of patient feedback were repeated after each sonication. In the patients who underwent the sham procedure, energy was disengaged, but the patients were also evaluated after each sham sonication. The focusing of the ultrasound beams was standardized to fit a lesion that was shaped and targeted in the dorsolateral subthalamic nucleus and immediately dorsally to impinge on the pallidothalamic tract. The ultrasound focus coordinates were adjusted according to clinical effects; details on the ultrasound subthalamotomy procedure in the active-treatment group are provided in Table S1 in the Supplementary Appendix.

OUTCOMES

There were two primary outcomes in this trial. The primary efficacy outcome was the between-group difference in the change from baseline to 4 months in the MDS-UPDRS III score for the more affected side of the body while patients were in the off-medication state (i.e., after a minimum 12-hour overnight withdrawal of antiparkinsonian drugs). The primary safety outcome (i.e., the incidence and severity of complications that occurred during the procedure or that were related to the procedure, according to the definition of adverse events from the Food and Drug Administration) was assessed at 4 months.

The primary efficacy outcome was ascertained with the MDS-UPDRS III.[14] Scores for one side of the body range from 0 to 44, with higher scores indicating greater motor impairment, and include subitems for rigidity, bradykinesia, and tremor. (Details about ascertainment of the score are provided in Section S2 in the Supplementary Appendix.) An exploratory visit occurred at 2 months, and the primary efficacy measures were determined at 4 months. Each patient was assessed at baseline and at the 2-month and 4-month visits by the same movement-disorder

neurologist (one of three specified investigators) who was unaware of the trial-group assignments.

We assessed safety by recording the frequency and severity of any adverse events that were reported by patients or that were observed during the procedure or at the trial visits at 2, 4, and 12 months (the 12-month assessment was performed only in patients who had received active treatment, either because of randomization assignment or crossover). A complication or worsening of a preexisting clinical condition after the procedure was considered to be an adverse event regardless of causality. Patients were assessed with the use of MRI after the procedure and with the use of neuropsychological examinations, including assessments of memory, language, executive functions, and behavior, at baseline and 4 months after the procedure. Clinical management after the procedure was undertaken by neurologists who were aware of the trial-group assignments. After 4 months, patients were told their trial-group assignment, and those in the control group were offered open-label ultrasound treatment.

The secondary outcomes at 4 months were the following: the change from baseline in the MDS-UPDRS III score for the more affected side while patients were in an on-medication state (typically assessed 30 to 60 minutes after the intake of usual morning oral medication); the change in the MDS-UPDRS III score for the more affected side in both the off-medication and on-medication states (unblinded evaluation); the change in the MDS-UPDRS III specific subscores for rigidity, bradykinesia, and tremor (scores range from 0 to 8, from 0 to 20, and from 0 to 16, respectively, with higher scores indicating greater severity in all cases) for the more affected side in both the off-medication and on-medication states; activities of daily living (assessed with the use of the MDS-UPDRS, part II, questionnaire; scores range from 0 to 52 with higher scores indicating greater disability); general motor condition (MDS-UPDRS III total score; scores range from 0 to 132, with higher scores indicating worse parkinsonism) in both the off-medication and on-medication states; motor complications as assessed with the MDS-UPDRS, part IV (scores range from 0 to 24, with higher scores indicating more frequent or disabling motor complications); quality of life (assessed with the use of the 39-item Parkinson's Disease Questionnaire summary index[15]; scores range from 0 to 100, with higher scores indicating poorer well-being); the Patients' Global Impression of Change (scores range from 1 [very much improved] to 7 [very much worsened][16]); and the change in the daily dose of levodopa equivalent (measured in milligrams per day), which was calculated according to established conversions.[17]

Patients who had received active treatment also underwent an unblinded evaluation of the MDS-UPDRS III score for the treated side in the off-medication state at 12 months. The change in the MDS-UPDRS III total score at 4 months, with adjustment for motor severity at baseline,[18] was also analyzed. A survey of patients and clinical assessors regarding the success of blinding of the trial-group assignments was conducted immediately after the procedure and at 4 months.

Additional evaluations included efficacy and safety in patients who were initially assigned to undergo the sham procedure and who crossed over to receive active treatment once the 4-month blinded follow-up was complete. Unblinded subthalamotomy took place within the first weeks after unblinding, and patients were followed for an additional 12 months after this second procedure, with exploratory visits at 2 months and 4 months. Other additional analyses were the time of dopaminergic drug withdrawal before the motor MDS-UPDRS assessment and the axial motor score, which was calculated as the sum of the MDS-UPDRS III subitems for axial features (scores range from 0 to 36, with nine subscores, each on a scale from 0 to 4, for the assessment of speech, facial expression, neck rigidity, ability to arise from a chair, gait, postural stability, posture, global spontaneity of movement, and lip or jaw tremor; higher scores indicate greater impairment) (see Section S2).

STATISTICAL ANALYSIS

The trial assessed the superiority of subthalamotomy as compared with a sham procedure. A sample size of 40 was calculated on the basis of the 53% motor improvement that was observed in our pilot study,[7] a potential effect of 30% in the control group, and an assumption that 20% of the patients would discontinue the trial. Thus, the trial had 99% power to show the superiority of subthalamotomy with regard to the primary efficacy outcome. Power calculations were based on Student's t-test, with a randomization ratio of 2:1 for assignment to undergo subthalamotomy or the sham procedure, at a two-sided alpha of

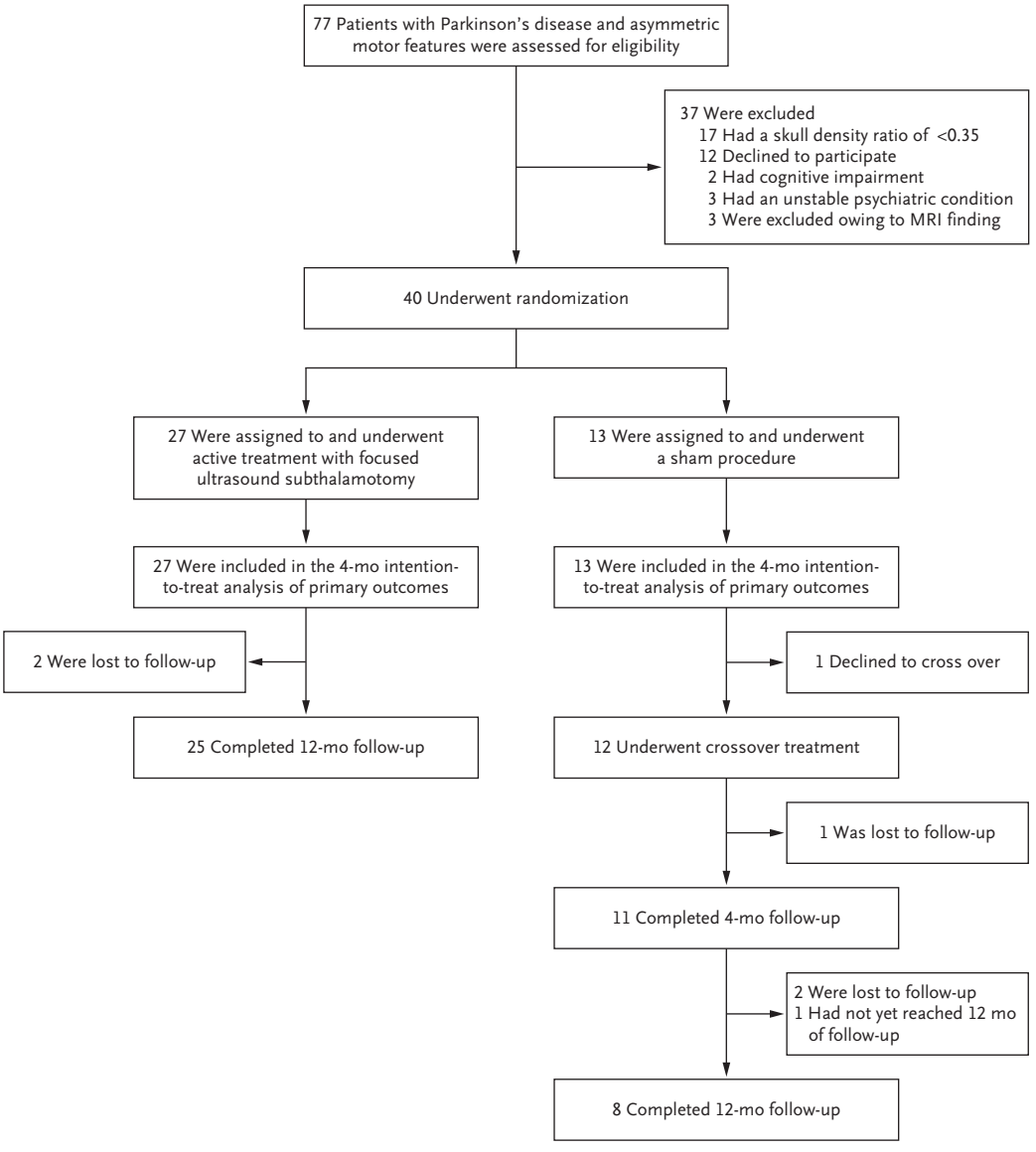

Figure 1. Enrollment and Follow-up of the Patients.

Patients who had a skull density ratio (an index of ultrasound penetration into the skull) of less than 0.35 were excluded from the trial. All 40 patients who had undergone randomization finished the blinded follow-up for the primary and main secondary outcomes (at 4 months). Of the 27 patients in the active-treatment group, 25 continued to the open follow-up phase for 12 months. Of the 13 patients in the control group (in which patients underwent a sham procedure), 12 crossed over to receive unblinded active treatment at 4 months. After undergoing the second (i.e., active) procedure, 11 patients in the crossover group completed an additional 4 months of follow-up and 8 patients completed 12 months of follow-up.

0.05. This sample size was also determined to be sufficient for the detection of procedure-related adverse events. The primary efficacy outcome was analyzed with a mixed model with repeated measures, including the independent effects of time point and baseline MDS-UPDRS III score for the more affected side. For each visit, the difference between the two groups and the change from baseline were estimated with the use of the least-squares means from the mixed model with repeated measures. The same model was applied to analyze all the secondary efficacy outcomes.

Descriptive statistics were calculated for the intention-to-treat population for all efficacy out-

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Focused Ultrasound Subthalamotomy (N=27)	Sham Procedure (N=13)
Age — yr		
Mean	56.6±9.3	58.1±8.8
Range	35–74	43–70
Sex — no. (%)		
Male	16 (59)	10 (77)
Female	11 (41)	3 (23)
Duration since diagnosis — yr		
Mean	5.6±2.5	7.3±3.8
Range	2–11	2–17
MDS-UPDRS III total score†‡		
Off-medication state	39.9±9.7	40.1±8.1
On-medication state	26.9±6.7	25.1±8.1
MDS-UPDRS III score for the more affected side of the body‡§		
Off-medication state	19.9±5.0	18.7±5.5
Rigidity	3.5±1.0	3.8±1.0
Bradykinesia	10.8±2.8	9.7±3.6
Tremor	5.6±3.0	5.2±2.2
On-medication state	14.2±4.2	11.9±5.1
Rigidity	2.6±1.1	2.6±1.4
Bradykinesia	7.9±2.9	6.4±2.9
Tremor	3.8±2.3	2.9±1.9
MDS-UPDRS IV score for levodopa-related motor complications¶	4.0±4.5	5.1±4.7
Dyskinesia	0.3±0.9	1.1±1.8
Motor fluctuations	3.0±3.1	3.5±2.8
Dystonia, in the off-medication state	0.7±1.2	0.5±1.1
MDS-UPDRS II score for activities of daily living‖	11.3±5.9	12.5±4.6
Treatment with levodopa — no. (%)**	26 (96)	12 (92)
Daily dose of levodopa equivalent — mg††	729.7±328.3	881.7±407.9
PDQ-39 summary index for quality of life‡‡	21.7±12.0	23.9±10.2

* Plus–minus values are means ±SD.

† Total scores on the Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS), part III, range from 0 to 132, with higher scores indicating more severe clinical features.

‡ The off-medication state was defined as a minimum 12-hour overnight withdrawal of antiparkinsonian drugs and a 24-hour withdrawal of prolonged-release formulations. The on-medication state was determined by both the patient and the clinician and indicated that the medication had been effective for at least 30 minutes after ingestion.

§ The MDS-UPDRS III score on the more affected side of the body was calculated as the sum of the assessments for rigidity (item 3.3; assessment on one side includes evaluation of rigidity in the upper and lower limbs on a scale from 0 to 8, with higher scores indicating higher rigidity) plus bradykinesia (items 3.4 to 3.8; assessment on one side includes evaluation of the upper and lower limbs on a scale from 0 to 20, with higher scores indicating more severe bradykinesia) plus tremor (items 3.15 to 3.17; assessment on one side includes evaluation of rest tremor in the upper and lower limbs and of postural and kinetic tremor in the upper limb on a scale from 0 to 16, with higher scores indicating more severe tremor). Thus, the overall score for one side ranges from 0 to 44, with higher scores indicating a worse motor condition.

¶ The score on the MDS-UPDRS, part IV, for levodopa-related motor complications ranges from 0 to 24, with higher scores indicating more severe or disabling motor complications. The score is calculated as the sum of the scores for dyskinesia in the on-medication state (items 4.1 and 4.2; range, 0 to 8), for motor fluctuations (items 4.3 through 4.5; range, 0 to 12), and for dystonia in the off-medication state (item 4.6; range, 0 to 4). In all patients, the assessment of dystonia in the off-medication state was restricted to the more affected side of the body.

‖ Scores on the MDS-UPDRS, part II, range from 0 to 52, with higher scores indicating more severe impairment in activities of daily living.

** Two patients were not taking levodopa at baseline. In one case, the patient had tried several dopaminergic drugs but had discontinued all of them because of side effects. The second patient was reluctant to start receiving levodopa therapy.

†† The daily dose of levodopa equivalent was calculated according to the accepted conversions of Tomlinson et al.[17]

‡‡ Scores on the 39-item Parkinson's Disease Questionnaire (PDQ-39) summary index range from 0 to 100, with higher scores indicating worse quality of life.

comes. Secondary outcomes were not adjusted for multiple comparisons, and no clinical inferences can be made from these data. No imputations were made for missing data, because all the patients were examined at 4 months for the primary outcome, and the secondary outcomes are presented descriptively. A two-sided P value of less than 0.05 was considered to indicate statistical significance. Statistical analyses were conducted with the use of SAS software, version 9.4 (SAS Institute), on a Windows 2016 terminal.

RESULTS

TRIAL PARTICIPANTS

A total of 77 patients were assessed for eligibility, and 40 patients (36 patients at CINAC and 4 at the University of Virginia Medical Center) were enrolled from March 2018 through May 2019 (Fig. 1). A total of 27 patients were assigned to undergo subthalamotomy and 13 to undergo the sham procedure. Overall, the mean (±SD) age of the patients was 57.1±9.1 years (range, 35 to 74), and the mean duration of disease was 6.2±3.0 years. The mean MDS-UPDRS III total score at baseline was 39.9±9.1 in the off-medication state and 26.3±7.2 in the on-medication state. The mean daily dose of levodopa equivalent at baseline was 777.9±358.1 mg.

The characteristics of the patients were similar in the two groups at baseline (Table 1), with the exceptions in the control group of an older patient age (58.1±8.8 years, vs. 56.6±9.3 years in the active-treatment group), a longer mean duration of disease (7.3±3.8 years vs. 5.6±2.5 years), a higher MDS-UPDRS IV dyskinesia score (1.1±1.8 vs. 0.3±0.9), and a higher mean daily dose of dopaminergic drug (881.7±407.9 mg vs. 729.7±328.3 mg of levodopa equivalent). In the active-treatment group, 16 patients underwent subthalamotomy in the left hemisphere and 11 in the right. In the control group, 7 patients underwent the sham procedure in the left hemisphere, and 6 in the right (Table S1).

PRIMARY EFFICACY OUTCOME

The active-treatment group had a decrease (indicating improvement) in the mean MDS-UPDRS III score for the more affected side from 19.9±5.0 at baseline to 9.9±4.9 at 4 months (least-squares mean difference, 9.8 points; 95% confidence interval [CI], 8.6 to 11.1), as compared with a decrease in the control group from 18.7±5.5 at baseline to 17.1±6.0 at 4 months (least-squares mean difference, 1.7 points; 95% CI, 0.0 to 3.5) (Fig. 2, Table 2, and Fig. S1). The primary effi-

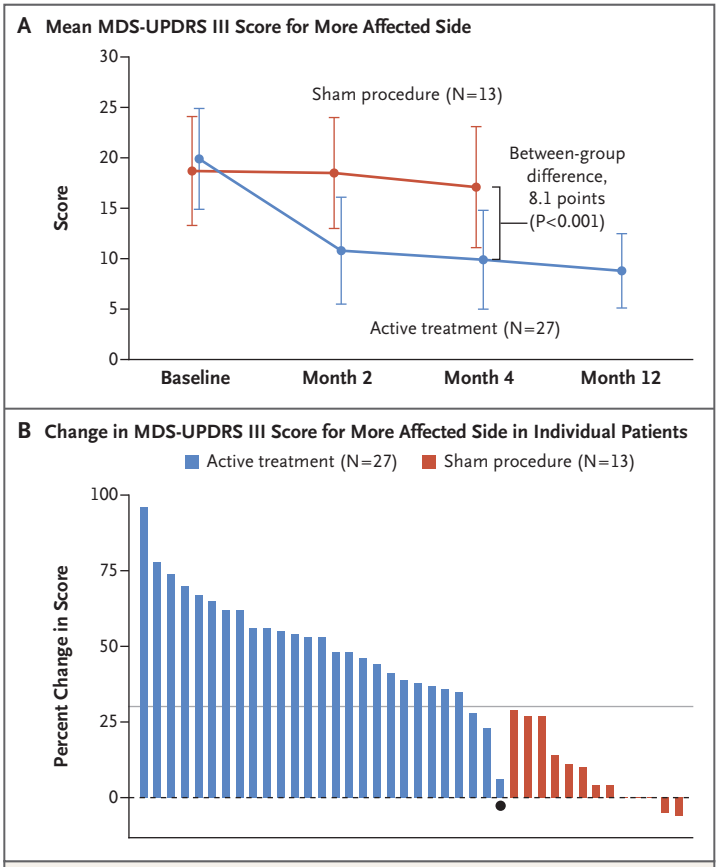

Figure 2. Clinical Outcomes of Focused Ultrasound Subthalamotomy, as Compared with a Sham Procedure, in One Hemisphere.

Panel A shows the mean Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor scores (part III) for the more affected side of the body in the off-medication state in the active-treatment group (in which patients underwent focused ultrasound subthalamotomy) and the control group (in which patients underwent a sham procedure). Scores are assessed on a scale from 0 to 44, with higher scores indicating higher motor impairment, and include subitems for rigidity, bradykinesia, and tremor. Patients in the active-treatment group had improvement 4 months after the procedure, with a decrease from a mean (±SD) score of 19.9±5.0 at baseline to 9.9±4.9 at 4 months. The change in the mean score was significantly superior with subthalamotomy than with the sham procedure (between-group difference in the least-squares mean change from baseline, 8.1 points; 95% CI, 6.0 to 10.3; P<0.001). The mean decrease in the score in the active-treatment group at 12 months was 11.6 points (95% CI, 9.9 to 13.3; among 25 patients with data available). I bars indicate the standard deviation. Panel B shows the changes in the MDS-UPDRS III score for the more affected side of the body in the off-medication state in individual patients, according to trial group. The line at 30% indicates the minimal clinically meaningful change.[19] Positive values in this graph indicate clinical improvement, and negative values indicate worsening of parkinsonism. The median improvement from baseline (dashed line) was 52.6% in the active-treatment group and 4.2% in the control group. In one patient (black circle), the procedure was aborted before completion owing to severe anxiety in the patient.

Table 2. Primary and Secondary Efficacy Outcomes, Assessed from Baseline to 4 Months (Intention-to-Treat Population).*

Outcome	Baseline		Within-Group Change from Baseline to 4 Mo				Between-Group Difference in Change
	Focused Ultrasound Subthalamotomy (N=27)	Sham Procedure (N=13)	Focused Ultrasound Subthalamotomy (N=27)		Sham Procedure (N=13)		
			mean (95% CI)	%	*mean (95% CI)*	%	*mean (95% CI)*
Primary efficacy outcome							
MDS-UPDRS III score for the more affected side, in the off-medication state	19.9±5.0	18.7±5.5	9.8 (8.6 to 11.1)	52.6	1.7 (0.0 to 3.5)	4.2	8.1 (6.0 to 10.3)†
Secondary efficacy outcomes							
MDS-UPDRS III score for the more affected side, in the on-medication state‡	14.2±4.2	11.9±5.1	6.4 (5.2 to 7.6)	46.5	0.1 (–0.3 to 0.6)	6.0	5.9 (3.8 to 8.0)
MDS-UPDRS III score for the more affected side in an unblinded evaluation							
Off-medication state	19.5±3.8	18.6±5.7	11.1 (9.9 to 12.3)	53.8	1.4 (0.3 to 2.4)	2.0	10.4 (8.3 to 12.5)
On-medication state‡	14.0±4.3	12.3±4.5	7.5 (6.4 to 8.6)	53.1	0.3 (–0.6 to 1.3)	2.9	6.6 (4.7 to 8.5)
MDS-UPDRS III subscores for more affected side							
Off-medication state							
Rigidity	3.5±1.0	3.8±1.0	1.9 (1.6 to 2.2)	60.0	0.1 (–0.3 to 0.6)	0.0	1.8 (1.3 to 2.3)
Bradykinesia	10.8±2.8	9.7±3.6	4.0 (3.2 to 4.7)	33.3	1.4 (0.3 to 2.4)	9.1	2.7 (1.4 to 4.0)
Tremor	5.6±3.0	5.2±2.2	4.0 (3.3 to 4.6)	83.3	0.3 (–0.6 to 1.3)	0.0	3.6 (2.5 to 4.8)
On-medication state‡							
Rigidity	2.6±1.1	2.6±1.4	1.3 (1.0 to 1.6)	50.0	–0.2 (–0.6 to 0.2)	0.0	1.5 (1.1 to 2.0)
Bradykinesia	7.9±2.9	6.4±2.9	2.3 (1.5 to 3.1)	27.3	0.8 (–0.3 to 2.0)	12.7	1.5 (0.1 to 2.9)
Tremor	3.8±2.3	2.9±1.9	2.7 (2.1 to 3.3)	92.9	0.0 (–0.8 to 0.9)	0.0	2.7 (1.6 to 3.7)
MDS-UPDRS II score	11.3±5.9	12.5±4.6	4.1 (2.2 to 5.9)	42.9	–1.4 (–4.0 to 1.2)	–11.8	5.5 (2.2 to 8.7)
MDS-UPDRS III total score							
Off-medication state	39.9±9.7	40.1±8.1	15.2 (13.5 to 17.0)	34.2	2.3 (–0.2 to 4.8)	6.3	12.9 (9.9 to 16.0)
On-medication state‡	26.9±6.7	25.1±8.1	8.4 (6.6 to 10.3)	33.9	–0.8 (–3.4 to 1.8)	0.0	9.2 (6.0 to 12.4)
MDS-UPDRS IV total score§	4.0±4.5	5.1±4.7	1.1 (0.0 to 2.1)	40.0	–1.2 (–2.7 to 0.3)	0.0	2.3 (0.5 to 4.1)
Dyskinesia	0.3±0.9	1.1±1.8	0.0 (–0.4 to 0.3)	NA	–0.4 (–0.9 to 0.2)	NA	0.3 (–0.3 to 1.0)
Motor fluctuations	3.0±3.1	3.5±2.8	0.9 (0.2 to 1.6)	26.8	–0.6 (–1.6 to 0.4)	12.5	1.5 (0.2 to 2.7)
Dystonia, in the off-medication state	0.7±1.2	0.5±1.1	0.2 (–0.1 to 0.5)	75.0	–0.2 (–0.6 to 0.2)	NA	0.4 (–0.1 to 1.0)
PDQ-39 summary index	21.7±12.0	23.9±10.2	7.4 (4.1 to 10.6)	38.5	1.6 (–3.1 to 6.2)	29.0	5.8 (0.1 to 11.4)
Daily dose of levodopa equivalent (mg)	729.7±328.3	881.7±407.9	–94.5 (–151.9 to –37.2)	7.5	22.5 (–60.2 to 106.4)	0.0	–117.0 (–218.0 to –16.0)
Additional analysis							
MDS-UPDRS III score for the more affected side in the open-label crossover subgroup¶	19.5±3.9	NA	11.6 (8.4 to 14.8)	68.0	NA	NA	NA

cacy outcome of the between-group difference in the change in the score for the more affected side in the off-medication state at 4 months was 8.1 points (95% CI, 6.0 to 10.3; P<0.001).

SAFETY OUTCOMES

Dyskinesia in the off-medication state developed in six patients in the active-treatment group (22%) in the first week after subthalamotomy (Table 3). One patient had lower-limb monoballism, and the other five patients had mild-to-moderate upper-limb chorea (in one patient), lower-limb chorea (in one), or hemibody chorea (in three). At 4 months, dyskinesia on the treated side in the off-medication state persisted in three patients (11%), who had dyskinesia in the foot, hand, or shoulder of the treated side of the body (Video 1). New-onset dyskinesia on the treated side in the on-medication state developed in an additional six patients (22%) in the active-treatment group, persisted in one patient at 4 months, and was present in two patients at 12 months. The 12-month outcomes in all the patients in whom dyskinesia developed are shown in Table S2.

Videos showing the effects of subthalamotomy are available at NEJM.org

Weakness on the treated side was present the day after active treatment in five patients (19%). In two patients, it was predominantly faciobrachial. One patient had distal strength of 2/5 and proximal strength of 3/5 in the upper limb (scores on the motor scale range from 0 [no movement] to 5 [normal power]; a score of 2/5 indicates slight movement and a score of 3/5 indicates that movement is possible against gravity but not against resistance); this patient also had 4/5 strength in the lower limb (movement against resistance but less than normal power). The other patient had 4/5 weakness on the more affected side of the body. At 4 months, both patients had scores of 4/5 in the distal upper limb and 5/5 in all other muscle groups. Strength in both patients had recovered at 12 months, but hand clumsiness and asymmetric stride persisted in both. The remaining three patients had mild (4+/5) hemiparesis that resolved within 4 weeks.

Three additional patients (11%) in the active-treatment group had isolated facial asymmetry, which was still present in 1 patient at 4 months. Speech disturbance developed in 15 patients (56%) in the active-treatment group and persisted in 3 patients at 4 months and in 1 patient at 12 months. Gait dysequilibrium was present after the procedure in 13 patients (48%) in the active-

* Plus–minus values are least-squares means ±SD. Because of the lack of a prespecified plan for adjustment of the 95% confidence intervals for multiple comparisons of secondary outcomes, no inferences can be made from these data. When the 95% confidence intervals for the between-group differences include zero, these differences are considered to be not significant. For the change values, both within a single group and between the two groups, positive values indicate a reduction (improvement), and negative values indicate an increase (worsening) in all scores. The exception is the daily dose of levodopa equivalent, in which negative values indicate a decrease in the dose and positive values an increase in the dose. The mixed model for repeated measures was fitted to evaluate the within-group and between-group differences. Results are presented as mean values with 95% confidence intervals; also shown is the median percentage change from baseline for each outcome. The P value corresponds to the analyses for the primary efficacy outcome (i.e., the between-group difference in the change in the MDS-UPDRS III score for the more affected side of the body). NA denotes not applicable.

† P<0.001.

‡ A total of 26 of the 27 patients in the active-treatment group and all patients in the control group received antiparkinsonian medication.

§ For the MDS-UPDRS IV score, all patients were included in the analysis of the within-group and between-group differences, regardless of their baseline score. For the estimation of percentage of change, we excluded from the analysis of each corresponding subitem any patients who scored 0 at baseline. Thus, for the percentage of change in the total MDS-UPDRS IV score, a total of 17 patients in the active-treatment group and 9 in the control group were included in the analysis; for motor fluctuation subitems, the analysis included 16 and 9 patients, respectively; and for dystonia in the off-medication state, the analysis included 8 patients in the active-treatment group. For dystonia in the off-medication state in the control group (which included 3 patients who had a score of >0 at baseline) and for dyskinesia (which included 4 patients in each group who had a score of >0 at baseline), the measurement of the percentage of change was not considered to be applicable owing to the small sample and is therefore not provided.

¶ A total of 12 patients crossed over from the control group to receive active treatment.

Table 3. Adverse Events.*

Adverse Event	Focused Ultrasound Subthalamotomy (N=27)					Sham Procedure (N=13)
	Total	At 24 Hr	At 2 Mo	At 4 Mo	At 12 Mo	At 4 Mo
Dyskinesia on the more affected side, in the off-medication state — no. of patients (%)						
Any event, regardless of severity	6 (22)	0	6 (22)	3 (11)‖	0‖	0
Chorea	5 (19)	0	5 (19)	3 (11)	0	0
Ballism	1 (4)	0	1 (4)	0	0	0
New-onset dyskinesia on the more affected side, in the on-medication state — no. of patients (%)	6 (22)	0	6 (22)	1 (4)	2 (7)	0
Weakness on the more affected side — no. of patients (%)	5 (19)	5 (19)	2 (7)	2 (7)	2 (7)**	0
Isolated facial asymmetry — no. of patients (%)	3 (11)	3 (11)	3 (11)	1 (4)	0	0
Speech disturbance — no. of patients (%)						
Any objective or subjective event†	15 (56)	6 (22)	12 (44)	3 (11)	1 (4)	0
Dysarthria, assessed objectively on examination	7 (26)	6 (22)	5 (19)	3 (11)	1 (4)	0
Slurred speech, as reported by the patient	8 (30)	0	7 (26)	0	0	0
Gait disturbance — no. of patients (%)						
Any objective or subjective event‡	13 (48)	8 (30)	7 (26)	2 (7)	1 (4)	0
Ataxia, assessed objectively on examination	3 (11)	2 (7)	1 (4)	0	0	0
Unsteady gait, as reported by the patient	10 (37)	6 (22)	6 (22)	2 (7)	1 (4)	0
Upper limb dysmetria — no. of patients (%)	2 (7)	0	2 (7)	0	0	0
Impulsiveness — no. of patients (%)	1 (4)	0	1 (4)	0	0	0
Weight gain — no. of patients (%)§	2 (7)	0	1 (4)	1 (4)	2 (7)	0
Somnolence — no. of patients (%)	1 (4)	1 (4)	0	0	0	0
Intraprocedural sensations or events, all transient — no. of patients (%)						
Nausea	7 (26)					2 (15)
Emesis	1 (4)					1 (8)
Dizziness	13 (48)					2 (15)
Head “tilting”	13 (48)					1 (8)
Head discomfort, such as “heat” or “pressure”	11 (41)					1 (8)
Anxiety	6 (22)					0
Pin-site head pain	16 (59)					8 (62)
Right inner ear pain	1 (4)					0
Headache	5 (19)					6 (46)
Back or neck pain	4 (15)					2 (15)
High blood pressure	7 (26)					6 (46)
Fatigue	1 (4)					1 (8)
Chest pain	0					1 (8)
Other adverse events not directly related to treatment — no. of patients (%)						
Rib fracture	2 (7)					0
Fall	2 (7)					0
Dysuria	1 (4)					0
Total adverse events, according to severity — no. of events¶	144					31
Mild	96					13
Moderate	40					16
Severe	8					2

Table 3. (Continued.)

* Shown are the total numbers and percentages of patients in the active-treatment group in whom each adverse event (transient or persistent) developed. The primary safety outcome was assessed at 4 months. All the patients in the active-treatment group had at least one adverse event. The "2-month" column includes adverse events that were observed at the 2-month visit or that were reported by patients as occurring between 24 hours and 2 months after the procedure. Adverse events in the unblinded cohort (i.e., the 12 patients who underwent subthalamotomy after the initial 4-month period) are listed in Table S10.

† Patients who reported "slurred speech" were those without any new speech disorder identified on the neurologic examination but who reported less fluency or greater difficulty in pronunciation while speaking.

‡ Patients who reported "unsteady gait" were those without any new observable balance disorder on the neurologic examination but who reported having less equilibrium while walking.

§ The weight increase was 5% (from 82.9 to 87.0 kg) in one patient and 7% (from 101.0 to 108.0 kg) in the other.

¶ The severity of adverse events was classified as follows: mild indicates an asymptomatic state or mild symptoms, with no or minimal interference with usual social and functional activities and with no intervention indicated; moderate indicates symptoms that cause greater than minimal interference with usual social and functional activities, with minimal, local, or noninvasive intervention indicated; and severe indicates symptoms that disrupt activities of daily living (inability to perform usual social and functional activities), with intervention or hospitalization indicated.

‖ Five of the six patients with dyskinesia in the off-medication state after treatment had dyskinesia in the on-medication state at 4 months. In two patients, it was still present in the on-medication state at 12 months of follow-up.

** Strength had recovered at 12 months, but hand clumsiness and asymmetric stride persisted on the treated side.

treatment group and persisted in 2 patients at 4 months, with persistent unsteadiness at 12 months in 1 patient. One patient in the active-treatment group had somnolence after the procedure, which resolved the next morning. Impulsive binge eating developed in another patient in the active-treatment group for 2 months after treatment; the condition resolved.

Intraprocedural adverse events such as headache and dizziness occurred in both groups but occurred more frequently in the active-treatment group than in the control group (Table 3); these events resolved after the procedure. Severe anxiety developed in one patient in the active-treatment group; the condition necessitated that the procedure be stopped before therapeutic thermal dosing was achieved. This patient was included in the analysis of all outcomes. Neurocognitive testing results at baseline and at 4 months are shown in Tables S3 and S4.

No complications of the active procedure were detected by MRI, except for perilesional edema, which resolved by 4 months in all the patients in this group (Fig. S2). There were no intracerebral hemorrhages.

SECONDARY AND OTHER OUTCOMES

Because of the lack of a prespecified plan to adjust the widths of the 95% confidence intervals for multiple comparisons, no clinical conclusions can be drawn from these data. The MDS-UPDRS III score for the more affected side in the on-medication state at 4 months decreased by 6.4 points (95% CI, 5.2 to 7.6) in the active-treatment group and by 0.5 points (95% CI, −1.2 to 2.2) in the control group (between-group difference, 5.9 points; 95% CI, 3.8 to 8.0). Other secondary outcomes, including the reduction in the dose of levodopa equivalent after the procedure, were in the same direction as the primary outcome with the exception of dyskinesia (measured as the sum of MDS-UPDRS IV subitems 4.1 and 4.2) and dystonia in the off-medication state (subitem 4.6), which did not differ between the two groups at 4 months (between-group differences, 0.3 points [95% CI, −0.3 to 1.0] and 0.4 points [95% CI, −0.1 to 1.0], respectively) (Table 2, Tables S5 and S6, and Fig. S3).

Clinical improvement according to the Patients' Global Impression of Change at 4 months was reported by 23 of 27 patients (85%) in the active-treatment group and by 2 of 13 patients (15%) in the control group (Figs. S4 and S5 and Table S7). The change from baseline to 12 months in the MDS-UPDRS III score for the more affected side among 25 patients with available data in the active-treatment group was 11.6 points (95% CI, 9.9 to 13.3). The association between disease severity at baseline and the absolute reduction in the MDS-UPDRS III total score 4 months after the procedure is shown in Table S8. The times of drug withdrawal before testing for motor assessment in the off-medication state were similar in the two groups (Table S9). Results of the additional outcome of axial motor function in all the patients are provided in Table S11.

Of the 27 patients in the active-treatment group, 26 correctly identified their trial-group assignment, both immediately after the procedure and at 4 months; in the control group, 9 of

the 13 patients correctly identified their trial-group assignment immediately after treatment, and 11 did so at 4 months. Investigators who were intended to be unaware of the trial-group assignments identified the actual assignment in all the patients.

In the open-label phase of the trial, 12 of the 13 patients in the control group crossed over to receive ultrasound subthalamotomy after the 4-month blinded assessment period. Among patients with available data, the mean MDS-UPDRS III score for the more affected side in this unblinded subgroup decreased from 19.5±3.9 at baseline to 8.1±5.3 at 4 months after unblinded treatment (least-squares mean difference, 11.6 points; 95% CI, 8.4 to 14.8; among 11 patients) and to 9.7±6.4 at 12 months (least-squares mean difference, 8.7 points; 95% CI, 4.5 to 12.9; among 8 patients). One patient was lost to follow-up at 4 months after undergoing the active procedure, and 4 patients were lost to follow-up at 12 months.

New-onset dyskinesia developed in three patients in the crossover subgroup. One patient had hemiballismus, which was considered to be a serious adverse event and which persisted as lower limb chorea in the off-medication state at 4 months. Exacerbation of preexisting levodopa-induced dyskinesia occurred in two patients, isolated facial asymmetry in one, speech disturbance in five, and gait imbalance in five. (Details regarding the crossover subgroup are provided in Fig. S6 and Table S10.)

DISCUSSION

This randomized, sham-controlled trial showed that focused ultrasound subthalamotomy performed in one hemisphere improved the motor features of Parkinson's disease on the more affected side at 4 months. Adverse events such as dyskinesias, motor weakness, and gait and speech disturbances were frequent and persisted in several patients. These results are similar to outcomes in uncontrolled series of stereotactic radiofrequency subthalamotomy for the treatment of Parkinson's disease.[20-24] The change from baseline in the MDS-UPDRS III score for the more affected side in patients who underwent active treatment varied, ranging from 5 to 95%; the changes were qualitatively more evident for reduction of tremor and rigidity than for bradykinesia.

Among the 27 patients in the active-treatment group, new-onset dyskinesia on the treated side occurred in 12 patients, persisted in 3 at the 4-month primary safety evaluation, and persisted in 2 at 12 months. An approach that has been suggested to reduce the risk of hemichorea and ballism has been to extend ablations dorsal to the subthalamic nucleus in order to interrupt the pallidothalamic-projecting neurons.[25,26] In patients with Parkinson's disease who are treated with subthalamic deep-brain stimulation, one aspect of the control of dyskinesias is the ability to reduce the dose of dopaminergic drug.[27] In the current trial, a comparison of the change in the mean dose of dopaminergic medication between the active-treatment group and the control group was in the same direction as the primary outcome (i.e., the reduction from baseline in the dose of levodopa equivalent was greater in the active-treatment group than in the control group); however, the 95% confidence intervals for this and other secondary outcomes were not adjusted for multiple comparisons, so no definite conclusions can be drawn from these data.

Subthalamotomy was performed in one hemisphere, and the natural evolution of Parkinson's disease eventually leads to motor impairment on both sides of the body in most patients. The likely need for an increase in the daily dose of levodopa equivalent to maintain function on the untreated side of the body could lead to the development of dyskinesias on the treated side. However, the few open-label studies of long-term (≥36 months) follow-up of radiofrequency subthalamotomy performed in one hemisphere do not provide support for this concern.[20-22]

This trial has limitations. The small sample size and the enrollment of almost all the patients at one of the two trial sites (36 patients at one site and 4 at the other) limits the generalizability of the results because the trial approximates a single-center trial. Patients and assessors correctly guessed the trial-group assignments, which eliminates the intended effect of blinding. Furthermore, because of the lack of a prespecified plan for adjustment of the 95% confidence intervals for multiple comparisons of secondary outcomes, no definite inferences can be made from these data.

In this trial involving a selected group of patients with markedly asymmetric Parkinson's disease, we found that focused ultrasound subthalamotomy performed in one hemisphere resulted in improved motor scores at 4 months but was associated with adverse events, including dyskinesias and other neurologic complications.

Longer-term and larger trials are needed to determine the role of focused ultrasound subthalamotomy in the management of Parkinson's disease and its effect as compared with other available treatments, including deep-brain stimulation.

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APPENDIX

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