MR-guided focused ultrasound pallidotomy for Parkinson’s disease: safety and feasibility

Howard M. Eisenberg, MD, Vibhor Krishna, MD, SM, W. Jeffrey Elias, MD, G. Rees Cosgrove, MD, Dheeraj Gandhi, MD, Charlene E. Aldrich, RN, MSN, and Paul S. Fishman, MD, PhD

Objective

Stereotactic radiofrequency pallidotomy has demonstrated improvement in motor fluctuations in patients with Parkinson’s disease (PD), particularly levodopa (L-dopa)–induced dyskinesias. The authors aimed to determine whether or not unilateral pallidotomy with MR-guided focused ultrasound (MRgFUS) could safely improve Unified Dyskinesia Rating Scale (UDysRS; the primary outcome measure) scores over baseline scores in patients with PD.

Methods

Twenty patients with PD and L-dopa responsiveness, asymmetrical motor signs, and motor fluctuations, including dyskinesias, participated in a 1-year multicenter open-label trial of unilateral MRgFUS ablation of the globus pallidus internus.

Results

The sonication procedure was successfully completed in all 20 enrolled patients. MRgFUS-related adverse neurological events were generally mild and transient, including visual field deficit (n = 1), dysarthria (n = 4, 2 mild and 2 moderate), cognitive disturbance (n = 1), fine motor deficit (n = 2), and facial weakness (n = 1). Although 3 adverse events (AEs) were rated as severe (transient sonication-related pain in 2, nausea/vomiting in 1), no AE fulfilled US FDA criteria for a Serious Adverse Effect. Total UDysRS, the primary outcome measure, improved 59% after treatment (baseline mean score 36.1, 95% CI 4.88; at 3 months 14.2, 95% CI 5.72, p < 0.0001), which was sustained throughout the study (at 12 months 20.5, 95% CI 7.39, 43% improvement, p < 0.0001). The severity of motor signs on the treated side (Movement Disorder Society version of the United Parkinson’s Disease Rating Scale [MDS-UPDRS] part III) in the “off” medication state also significantly improved (baseline mean score 20.0, 95% CI 2.4; at 3 months 10.6, 95% CI 1.86, 44.5% improvement, p < 0.0001; at 12 months 10.4, 95% CI 2.11, 45.2% improvement, p > 0.0001). The vast majority of patients showed a clinically meaningful level of improvement on the impairment component of the UDysRS or the motor component of the UPDRS, while 1 patient showed clinically meaningful worsening on the UPDRS at month 3.

Conclusions

This study supports the feasibility and preliminary efficacy of MRgFUS pallidotomy in the treatment of patients with PD and motor fluctuations, including dyskinesias. These preliminary data support continued investigation, and a placebo-controlled, blinded trial is in progress.

Clinical trial registration no.: NCT02263885 (clinicaltrials.gov)

Keywords

MR-guided focused ultrasound; MRgFUS; pallidotomy; Parkinson’s disease; dyskinesia; functional neurosurgery

Stereotactic surgery targeting the globus pallidus internus (GPI) has been shown to benefit motor symptoms of Parkinson’s disease (PD).1-3 Radiofrequency pallidotomy results in a particularly substantial decrease in involuntary movements known as dyskinesias, induced by long-term treatment with carbidopa/levodopa (L-dopa) (L-dopa–induced dyskinesias).4,5 Cardinal motor signs of PD such as tremor, bradykinesia, and rigidity are also improved contralateral to a pallidotomy, specifically in the “off” L-dopa state in patients with a fluctuating response to L-dopa.6-8 Deep brain stimulation (DBS) of the GPI was intro-
duced in part to reduce the neurological complications of radiofrequency pallidotom y, such as weakness, imbalance, cognitive abnormalities, and visual field defects.\textsuperscript{9-14} Beneficial effects of GPI DBS that are similar to those of pallidotomy are well documented using this strategy, which employs high-frequency stimulation rather than a destructive brain lesion to ameliorate motor symptoms of PD.\textsuperscript{15-18} DBS is still an open surgical procedure, and similar to radiofrequency, pallidotomy shares the risk of intracranial bleeding and infection.\textsuperscript{9,20} Another limitation of DBS is that some appropriate patients find this form of open brain surgery, with the permanent implantation of its associated hardware, unacceptable.\textsuperscript{21}

MR-guided focused ultrasound (MRgFUS) is an incisionless method that can create a highly targeted brain ablation. MRgFUS of the ventral intermediate nucleus of the thalamus was initially FDA approved for the treatment of medically refractory essential tremor, and very recently for tremor-predominant PD as well. MRgFUS has also been utilized in the treatment of other motor aspects of PD, including dyskinesias.\textsuperscript{22-25} An initial patient report of successful unilateral lesioning of the GPi was followed by a small open-label study of PD patients with dose fluctuation including dyskinesia, which showed similar results to radiofrequency pallidotomy.\textsuperscript{26,27} On the basis of previous experience with radiofrequency pallidotomy and MRgFUS for PD and related movement disorders, we initiated a trial of MRgFUS unilateral pallidotomy for patients with asymmetrical motor signs and functionally interfering motor fluctuations, including bothersome dyskinesias.

**Methods**

**Study Population and Criteria**

Patients with a diagnosis of PD in the study had the following inclusion criteria: age between 40 and 80 years, and L-dopa–responsive PD with at least a 30% difference in motor score severity on part III of the Movement Disorder Society version of the United Parkinson’s Disease Rating Scale (MDS-UPDRS) between “on” and “off” medication states. Patients had a minimum severity in the “off” state with a motor score of at least 30 on part III of the MDS-UPDRS. This study was registered with the ClinicalTrials.gov database (http://clinicaltrials.gov), and its registration no. is NCT02263885.

PD motor symptoms were either unilateral or markedly asymmetrical, with predominant disability from one side of the body to the extent that the investigator felt there was a likelihood of improvement with unilateral treatment. All patients had functionally interfering motor fluctuations with dyskinesia on optimal and stable medical therapy with a score of at least 3 in response to question 4.2 of the MDS-UPDRS.

Exclusion criteria included suspicion of another related neurodegenerative disease (such as progressive supranuclear palsy, multisystem atrophy, or dementia with Lewy bodies); impaired cognition with a Montreal Cognitive Assessment score of less than 21; impairment of speech or swallowing (score of 3 or 4 on question 5 of part II of the MDS-UPDRS); impairment of balance with a score of 3 or greater on the Hoehn and Yahr scale; poorly controlled depression (Beck Depression Inventory score > 14); and significant medical or psychiatric comorbidities. Patients with vascular or structural lesions on MRI, a skull density ratio (i.e., the ratio of density of cortical bone to density of cancellous bone) of 0.40 or less, claustrophobia, or inability to lie flat were also excluded.

**Evaluation and Testing**

Preprocedure evaluations included physical and neurological examinations, comprehensive neuropsychological testing, formal visual field testing, S-UPDRS in both “on” and “off” states, and the Unified Dyskinesia Rating Scale (UDysRS).

Imaging evaluation obtained prior to the procedure included a noncontrast head CT scan as well as MRI of the brain. CT images reconstructed using a C-filter in bone windows were utilized for skull density measurements, identifying and marking calcifications, and procedural planning. Multiplanar MRI was performed for procedural planning. The following sequences were used for targeting and preplanning purposes: fast gray matter acquisition T1 inversion recovery (FGATIR) in 15 patients, 3D T1-weighted gradient echo in 3 patients, and T2-weighted fast spin echo in 2 patients. The axial images were reformatted or obtained in the commissural (anterior commissure–posterior commissure) plane.

**MRgFUS Pallidotomy Procedure**

MRgFUS pallidotomy was performed using the InSightec ExAblate 4000 Transcranial System interfaced with a 3T GE Medical System MRI machine. The patient’s head was shaved on the day of the procedure. After administration of local anesthetic, an Integra CRW stereotactic frame was placed on the patient’s head. A silicone membrane bag was placed around the head and connected to a circulating degassed and cooled water bath to create an air-free interface between the transducers and the head. The patient was placed supine and the head was affixed to the focused ultrasound device throughout the procedure. Intraoperative MRI of the brain was performed, and the intraoperative images were coregistered with the preoperative planning study. Targeting was performed using a combination of standard stereotactic coordinates for the GPi (20 mm lateral of midline, 3–4 mm anterior of midpoint, and 3 mm interior of the intercommissural line) and direct imaging of the GPi (Fig. 1 left). In 12 patients, direct imaging of the GPi using FGATIR MRI sequences as well as tractography of the corticospinal tract was utilized to adjust the ablation location. Initially, low-energy sonications were delivered to the target GPi, contralateral to the side of the desired treatment effect. As has been previously described, focused ultrasound lesioning was performed by initially heating an approximately 2-mm-diameter volume of tissue with short low-energy sonications generating a 40°C–45°C target temperature.\textsuperscript{23} The energy delivered was gradually increased, progressing incrementally to higher ablative temperatures, with each therapeutic sonication followed by patient evaluation for both improvement of motor symptoms of PD (rigidity, tremor, bradykinesia, ...
and dystonia, because patients were treated in the “off” medication state) and potential off-target adverse effects such as dysarthria, weakness, or vision changes. Transient improvement without off-target adverse effects with sublethal sonications was followed by sonications with increased energy to reach target temperatures greater than 56°C. The size and location of the ablative zone were also continuously monitored using MR thermometry.

Multiple lesions (typically 2–3), usually contiguous, were created guided by the boundaries of the GPi on MRI and the clinical response of the patient. Patients were awake during the procedure but were medicated as needed for procedure-related pain and nausea. Following the treatment session, the stereotactic frame was removed. The patients were observed overnight and discharged from the hospital the following day. A postprocedure MRI of the brain was acquired prior to discharge to evaluate the location and size of the lesion within the pallidum. Not all patients attained the target temperature of 56°C, but all treated patients had a lesion detectable by MRI immediately after the procedure and at least one sonication greater than 51°C (Fig. 1).

Adverse Events

The severity of adverse events (AEs) was predefined as mild (minor inconvenience, not affecting daily routine activities), moderate (bothersome, interferes with routine daily activities), or severe (incapacitating, cannot perform activities of daily living). The severity rating (mild, moderate, or severe) reflects the maximal severity of the occurrence at any time. Serious Adverse Effects (SAEs) fulfilled the FDA definition of serious, which is an injury or illness that 1) is life-threatening; 2) results in permanent impairment of a body function or permanent damage to a body structure; or 3) necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure. Permanent means irreversible impairment or damage.

Results

Patient Demographics

Of 34 patients initially screened, 20 were enrolled and treated in the study. These patients included 13 men and 7 women, of whom 18 were White and 2 were Hispanic, with a mean age of 56.4 years (range 35–74 years). The mean time from diagnosis was 9.9 years, and the mean daily L-dopa equivalent of therapy was 1039 ± 601 mg (Table 1). All 20 of the treated patients completed the 3-month visit. One patient withdrew following the 3-month visit for personal reasons. Nineteen patients were expected to attend the 6-month visit; 1 was unable to attend but continued participation. One patient withdrew following the 6-month visit to have an alternative treatment. For the 12-month visit, 18 patients were expected to attend but 1 was unable to attend. All patient and visit data are included in the analysis and figures.

MRgFUS Treatment Characteristics

Patients received a mean of 15 ± 3 sonications during treatment with a mean power of 605.6 ± 164.9 W. The mean maximum sonication power was 1045.1 ± 233.3 W.

Clinical Outcomes: Efficacy

The primary efficacy outcome measure, the total UDDysRS score at 3 months, significantly improved from a baseline score of 36.1 ± 11.12 (95% CI 4.88) to 14.2 ± 13.06

<table>
<thead>
<tr>
<th>Table 1. Demographics and baseline characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Sex (n = 20)</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>Race (n = 20)</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Black</td>
</tr>
<tr>
<td>Hispanic</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Age, yrs (n = 20)</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>SD</td>
</tr>
<tr>
<td>Max</td>
</tr>
<tr>
<td>Min</td>
</tr>
<tr>
<td>Yrs since diagnosis (n = 6)</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>SD</td>
</tr>
<tr>
<td>Max</td>
</tr>
<tr>
<td>Min</td>
</tr>
<tr>
<td>Daily L-dopa equivalents (n = 19), mg</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>SD</td>
</tr>
<tr>
<td>Max</td>
</tr>
<tr>
<td>Min</td>
</tr>
</tbody>
</table>

FIG. 1. Axial FGATIR sequence at day 1 (left) and 6 months (right) after treatment. The lesion (large arrow in both panels) is demonstrated as hyperintensity confined to the ventral lateral aspect of the GPi, with a smaller size of the T2 hyperintense lesions and resolution of the perilesional edema noted later on the follow-up image (right). The smaller arrow in the left panel indicates the internal lamina between the external and internal segments of the globus pallidus.
An improvement of 59% (p < 0.0001 using a paired t-test). This improvement continued throughout the duration of the study with a mean total UDysRS score at 12 months of 20.5 ± 15.99 (95% CI 7.39), a 43% improvement (p < 0.0001; Fig. 2A).

Similar improvement was seen in part III of the UDysRS, which is the examiner rating of dyskinesia intensity, with a reduction from a mean of 10.2 ± 6.17 (95% CI 2.0) to 4.5 ± 4.87 (95% CI 2.14) at 3 months, an improvement of 56.4%. This improvement also persisted, with a mean value of 4.4 ± 5.17 at 12 months (95% CI 2.39), for a reduction of 68.6% (Fig. 2B).

The efficacy of the treatment of motor signs of PD was assessed through the motor examination section (part III) of the MDS-UPDRS for those portions related to the treated side (9 items for arm and leg) in the “off” medication state. There was a significant reduction of scores from a baseline of 20.0 ± 5.62 (95% CI 2.46) to 10.6 ± 4.24 (95% CI 1.86) at 3 months after treatment, representing a 44.5% improvement (p < 0.0001). This significant reduction was sustained at 12 months after treatment, with a mean score of 10.4 ± 4.57 (95% CI 2.11), representing a 45.2% reduction from the baseline value (p < 0.0001; Fig. 2C).

Motor complications of PD were assessed with part IV of the MDS-UPDRS capturing data regarding duration and functional impact of both dyskinesias and “off” periods. After treatment there was a significant and persistent improvement in scores on this measure. The baseline pretreatment mean value of 11.1 ± 5.61 (95% CI 2.46) improved to 6.4 ± 4.15 (95% CI 1.82, p = 0.007) by 3 months and was maintained at this value (6.4 ± 4.31, 95% CI 1.99) at 12 months, representing a 42% improvement (Fig. 2D). No difference in results could be discerned between centers; however, the study was not powered to detect such differences.

In these patients with asymmetrical motor signs, even the unilateral treatment provided resulted in significant improvement in motor aspects of experiences of daily living as assessed by part II of the MDS-UPDRS. Treatment was followed by a significant reduction in mean score from 14.0 ± 7.53 (95% CI 3.30) at baseline to 7.4 ± 5.04 (95% CI 2.21, p = 0.007) at 3 months, an improvement of 47%. This group change was not sustained, worsening to 12.1 ± 6.5 (95% CI 2.99) by 12 months after baseline.

**Individual Patient Therapeutic Benefit or Worsening: Responder Analyses**

To obtain a measure of individual patient treatment success or failure, responder analysis was performed. Although most patients tolerate a dyskinetic state better than the bradykinesia state, there is individual patient variation as to the relative importance of improving cardinal Parkinsonian signs over the dyskinetic state. Achieving either of these outcomes may be important depending on the patient’s treatment objectives. For this responder analysis, a responder is a patient with a minimal clinically important improvement on...
either the UDysRS part III impairment score (2.32 points, while worsening scores are 2.76) or the MDS-UPDRS part III motor examination (3.25 points, while worsening scores are 4.63), as defined in previous studies.\textsuperscript{30–32}

The majority of patients were responders at all postprocedure evaluations, based on the UDysRS part III impairment scores, suggesting a meaningful clinical benefit in reduction in dyskinesias (70\% at 3 months, 68\% at 6 months, 76\% at 12 months). The majority of patients were also responders at all postprocedure evaluations based on the MDS-UPDRS part III motor examination scores, suggesting clinically meaningful relief of cardinal signs of PD, including tremor, bradykinesia, and rigidity (80\% at 3 months, 68\% at 6 months, 76\% at 12 months). The vast majority of patients had clinically important levels of improvement at all postprocedure evaluations on at least one of these two outcome measures (90\% at 3 months, 95\% at 6 months, 94\% at 12 months). One patient had a clinically important level of worsening at only the 3-month evaluation, based on the MDS-UPDRS part III.

In this study, screening scores were also used as baseline scores, so that follow-up scores for all outcome measures were compared to this single time point. In this setting it is possible that the initial single score may represent an atypically severe patient state and that improvement seen in follow-up scores may be influenced by the regression to the mean phenomenon. We feel that this phenomenon did not substantively influence the significant improvement seen in this study because improvement was noted in multiple outcome measures over multiple follow-up time points. A trend of diminishing improvement over time in the UDysRS score would be expected with disease progression.

Safety and Tolerability

A total of 61 AEs were reported by 17 patients (3 patients reported no AEs). Twenty-five of these AEs (41\%) were reported to be unrelated to the procedure, although 4 AEs (all mild) were considered to be related to placement of the stereotactic frame (headache, facial edema). Ten AEs were considered to be PD related.

Of the 36 procedure-related AEs, the most common were nausea/vomiting (n = 3), headache (n = 3), and sonication-related head pain (n = 7). Seventeen of the AEs were transient, which included the only severe AEs (2 with transient sonication-related head pain, 1 with transient nausea and vomiting, 5\% of total). Neurological AEs related to the procedure included visual field deficit (1 mild, transient), dysarthria (4 total, 2 mild and 2 moderate), cognitive disturbance (1 mild), fine motor deficit (2 mild), facial weakness (1 mild), and balance difficulties (1 moderate).

Twenty AEs persisted and continue to be followed, including fine motor difficulties (1 mild), dysarthria (1 mild, 2 moderate), and balance difficulties (1 mild), none of which were rated as severe. No AEs fulfilled FDA criteria of an SAE.

Discussion

This preliminary study of unilateral MRgFUS pallidotomy for the motor fluctuations and L-dopa–induced dyskinesia associated with PD demonstrated improvements in both “on” and “off” medication ratings. As the study’s primary clinical endpoint, total UDysRS assessments were improved by 59\% at 3 months following the procedure. Similarly, the motor signs of PD, as assessed from part III of the UPDRS contralateral to the lesion, improved by 44\% at 3 months and were maintained at 1 year. Safety is suggested by the mild and transient nature of the AEs reported.

Stereotactic lesioning of the GPi had been shown in multiple studies to result in significant and long-lasting improvement of motor signs and symptoms of PD, including dose fluctuations and L-dopa–induced dyskinesia.\textsuperscript{4–8} Although DBS is the current surgical standard of care for PD, preferred over radiofrequency pallidotomy, it has risks associated with all open surgical procedures of the brain, particularly bleeding and infection.\textsuperscript{19,20}

Previous studies involving patients with essential tremor and tremor-predominant PD have established that MRgFUS thalamotomy is an emerging alternative to DBS for patients with a medically refractory tremor.\textsuperscript{22–25} This study was designed to investigate if MRgFUS pallidotomy could provide benefits like radiofrequency pallidotomy and pallidal DBS, while reproducing the high level of safety and tolerance of MRgFUS of the thalamus seen in patients with essential tremor.\textsuperscript{33}

Our experience is also consistent with the previous limited reports of MRgFUS pallidotomy in PD. A 55-year-old woman with PD was initially reported by Na et al. to show a 62\% reduction in baseline UDysRS score 3 months after a unilateral MRgFUS-mediated pallidotomy and a 61.9\% reduction in motor “off” scores with no AEs.\textsuperscript{29} In a recently published study by Jung et al.,\textsuperscript{28} 10 patients with PD underwent unilateral MRgFUS pallidotomy. Of the 8 patients who successfully completed the procedure (in 2 patients thermal ablation could not be achieved, likely due to poor transcranial acoustic transmission), there was an improvement in total UDysRS by 52.7\% and a 30.2\% reduction in UPDRS “off” scores at 6 months.\textsuperscript{28} This is very similar to the percentage reductions in the total UDysRS and MDS-UPDRS part III in the “off” state in our study. This magnitude of improvement in motor “off” state and dyskinesia is also comparable to that seen in studies of radiofrequency open stereotactic pallidotomy.\textsuperscript{4–8} This amount of reduction in dyskinesias and motor “off” scores persisted through the 12-month duration of the study and is also clinically important, along with a meaningful reduction in functional interference by motor symptoms in the majority of treated patients.\textsuperscript{30–32}

The safety profile of our study of MRgFUS pallidotomy is also consistent with previous work investigating its application for tremor. There were no SAEs (as defined by the US FDA) in our 20 patients who underwent the procedure. Of the 61 AEs reported, only 3 (5\%) were rated as severe, and all of these were transient (headache, pain, nausea). Because the intent of MRgFUS is to create a permanent brain ablation, possible neurological deficits due to damage to brain tissue adjacent to the target are a clear concern. Neurological deficits accounted for only 10 of the 61 reported AEs, 7 of which were considered mild and none were rated as severe. Five of these deficits persisted for at least the duration of the study. With regard
to neurological deficits that had been previously associated with radiofrequency pallidotomy, only 1 patient had a mild visual field abnormality by confrontation that was not detectable by later formal visual field analysis. Another patient noted memory difficulties and showed decline on one subtest of a neuropsychological battery, but improvement on another subtest. This experience is consistent with an analysis of the safety of MRgFUS-mediated thalamotomy for essential tremor, where the vast majority of thalamotomy-related neurological AEs were mild and rarely severe.33

As expected for this incisionless procedure, no intracranial bleeding or infection occurred. The results of this initial study compare very favorably to those of previous studies of radiofrequency pallidotomy for PD, in which up to several percent of patients showed reportable neurological deficits that were serious and persistent. Although the total number of patients who have undergone MRgFUS pallidotomy, including our study, is relatively small, the current experience suggests an acceptable safety profile. This early experience is also encouraging because application of advancing imaging technology with improvements in targeting has the potential to improve the safety and efficacy of the procedure.34

Conclusions

The results of this initial study with regard to both efficacy and safety support our ongoing approach of expanded clinical investigation in the form of an adequately powered, blinded, controlled study of MRgFUS pallidotomy in the treatment of patients with significantly asymmetrical PD and a fluctuating motor response to medications, including dyskinesia. Successful development of this technology will provide patients with PD with a new, less-invasive treatment option.

References


Disclosures

Funding for the study presented was provided by InSightec Inc., the Focused Ultrasound Foundation, and the Michael J. Fox Foundation for Parkinson’s Research. Dr. Elias reports being a consultant for Second Sight.

Author Contributions

Conception and design: Fishman, Eisenberg, Elias. Acquisition of data: all authors. Analysis and interpretation of data: Fishman, Eisenberg, Krishna, Elias, Cosgrove, Gandhi. Drafting the article: Fishman, Eisenberg. Critically revising the article: Fishman, Eisenberg, Krishna, Elias, Cosgrove, Gandhi. Reviewed submitted version of manuscript: Fishman, Eisenberg, Krishna, Elias, Cosgrove. Approved the final version of the manuscript on behalf of all authors: Fishman. Administrative/technical/material support: Elias, Cosgrove, Gandhi, Aldrich. Study supervision: Eisenberg, Krishna, Elias, Cosgrove, Aldrich.

Correspondence

Paul S. Fishman: University of Maryland School of Medicine, Baltimore. pfishman@som.umaryland.edu.