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Pallido-Thalamic Tractotomy with Magnetic Resonance-Guided Focused Ultrasound (MRg-FUS) in Parkinson's Disease Patients

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Abstract

Magnetic resonance-guided focused ultrasound (MRgFUS) VIM thalamotomy was approved by the FDA and EMA in 2016 as an effective therapy for essential tremor patients (ET). However, there is a debate regarding the brain target for PD-resistant tremor patients (subthalamus, VIM-thalamic nucleus, associative tracts) to be treated with MRg-FUS in these patients. Some studies treating PD-resistant tremor with MRg-FUS in VIM and STN nucleus describe the efficacy on tremor, but also show adverse effects such as dyskinesia and motor deficits in the treated limb, along with a low impact on the quality of life of these patients. Associative tracts of the basal ganglia, particularly the pallido-thalamic and pallido-subthalamic tracts, have been chosen as targets in the past for ablative lesions by radiofrequency to treat PD patients with resistant tremor to oral therapy and motor fluctuations, with good outcomes but some adverse effects.

We present a prospective 12-month follow-up of 10 PD predominant-tremor patients resistant to oral medication who underwent MRg-FUS ablative lesions of the most rostral and ventral VIM thalamic region, located at the border between the thalamus and the zona incerta (cZI), just below the VIM thalamic nucleus. All the cardinal symptoms of PD separately (tremor, rigidity, and bradykinesia), as well as the impact of this therapy on their activities of daily living, were evaluated over a 12-month follow-up period.

Keywords: *Magnetic Resonance-Guided Focused Ultrasound (MRgFUS); Essential Tremor Patients (ET); Zona Incerta (cZI); Parkinson's Disease*

Introduction

Magnetic resonance-guided focused ultrasound (MRgFUS) VIM thalamotomy was approved by the FDA and EMA in 2016 as an effective therapy for essential tremor patients [1]. In recent years, there has been extensive medical information published regarding the benefits of MRg-FUS for essential tremor patients, providing data on the effectiveness and tolerance of this minimally invasive therapy. However, there is ongoing debate among neurological groups worldwide about the benefits of different brain targets (subthalamus, VIM-thalamic nucleus, associative tracts) to be treated with MRg-FUS in Parkinson's disease (PD) patients, in order to improve not only tremor but also other motor and non-motor symptoms.

Historically, PD patients with drug-resistant tremor have been treated with invasive therapies such as VIM-thalamotomy by radiofrequency or Deep Brain Stimulation (VIM-Thalamic or Luys subthalamic nucleus) with excellent outcomes. However, these treatments have faced criticisms due to exclusion criteria such as age, cognitive decline, and comorbidity, which limit their applicability in certain cases. There are also concerns about adverse effects and high costs, which may be unsustainable in low-income countries [2-4].

There is some published data on PD predominant-tremor patients treated with MRg-FUS, where ablative unilateral lesions in the VIM thalamic nucleus or STN have been performed. These studies describe the efficacy on tremor and provide detailed information on the outcomes of other cardinal symptoms of PD, such as rigidity and bradykinesia. Adverse effects such as dyskinesia and motor deficit in the treated limb have been observed, along with a low impact on the quality of life of these patients [5-9].

In the past, associative tracts of the basal ganglia, particularly the pallido-thalamic and pallido-subthalamic tracts, have been chosen as targets for ablative lesions by radiofrequency to treat PD patients with resistant tremor to oral therapy, as well as advanced PD patients with motor fluctuations and dyskinesias. These treatments have shown good outcomes in some patient series, but have also been associated with adverse effects and persisting dyskinesias in the ablative lesion of the subthalamic nucleus of Luys [10,11].

In the last three years, excellent results have also been reported in PD patients undergoing tractotomies, with at least one year of follow-up, showing positive outcomes.

In this article, we present a prospective 12-month follow-up of 10 PD predominant-tremor patients resistant to oral medication who underwent MRg-FUS ablative lesions of the most rostral and ventral VIM thalamic region, located at the border between the thalamus and the zona incerta (cZI), just below the VIM thalamic nucleus.

We evaluated all the cardinal symptoms of PD separately (tremor, rigidity, and bradykinesia), as well as the impact of this therapy on their activities of daily living over a 12-month follow-up period.

Patients and Methods

Ten patients who met the Brain bank Queen Square-UK criteria for Parkinson's disease (PD) with tremor resistant to common oral medications were selected for MRg-FUS thermolesion in the pallido-thalamic tract. This tract is located in the area adjacent to the contralateral VIM thalamic nucleus, which corresponds to the hemibody being treated. At baseline, the patients had a mean age of 65 years (range 41-82), mean disease onset of 7.5 years, and Hoehn and Yahr stages 2 and 3. The Swan and England scale ranged from 70% to 90% (Table 1). All patients exhibited asymmetric parkinsonism and had a mean UPDRS III sub-scale score of 27.8 and a mean score of 16.5 for the hemibody being treated. The postural tremor had a mean score of 3.4 on the Glass Tremor scale, and the resting tremor of the hemibody being treated had a mean score of 2.3. Both types of tremors were resistant to oral therapy, including anticholinergics, dopaminergic agonists, and l-dopa (mean dose of 525 mg dopa/carbidopa). The neurophysiological features of the tremor (amplitude and frequency) were assessed using EMG and accelerometry at baseline, the final evaluation, and the 12-month evaluation [10].

Cranial MRI and CT datasets were co-registered, and stereotactic planning was performed on an external workstation using BrainLab Elements® software (BrainLab TM, Munich, Germany). Cartesian coordinates were determined to focus on acquiring images for neuronavigation and co-registering them with the previously acquired cranial CT to identify the anterior and posterior commissures and midline.

Age	Onset years	Gender F/M	H-Y	S-E%	UPDRS III Total	UPDRS III partial	Glass tremor Scale
41	4	M	2	90	43	17	4
42	6	F	2	90	38	15	3
73	11	M	3	80	31	18	3
48	6	m	2	90	29	19	3
82	14	F	3	70	44	21	4
73	11	m	2	80	39	11	3
74	7	M	2	90	37	16	4
72	6	m	2	100	49	17	4
73	5	m	2	90	36	15	3
72	5	f	3	90	32	16	3
Mean 65	7,5	3/7	2,3	80,7	37.8	16,5	3,4

Table 1: *Demographic features.*

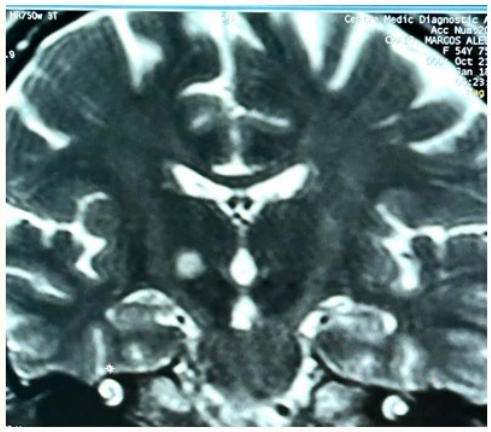
The coordinates were planned to extend the lesion to a more rostral and inferior area from the VIM thalamic nucleus, creating a larger ablative lesion that could extend from the VIM thalamic nucleus to the ZI in the Forel fields (H1 and H2), where the pallido-thalamic tract passes between the thalamus and the sub-thalamic nucleus. The estimation of the coordinates varied depending on the length of the ac-pc intercommissural line and the volume of the third ventricle. However, we theoretically considered 1.5 mm inferior to the VIM thalamic nucleus and 7 to 8 mm anterior to the posterior commissure (Picture 1).

A mean of eight successive sonications with progressively increasing intensity were applied in four stages: Anatomical Alignment, Clinical Verification, Low Power Treatment, and High-Power Treatment (58º-62º Celsius). Throughout the process, the effect on symptoms and the absence of acute undesirable effects were comprehensively checked. The sonications had a mean duration of 14.7 seconds.

The primary endpoints were the differences in assessment methods between the baseline evaluation and the final evaluation at the 12-month clinical visit during the follow-up. Sub-total UPDRS part III scale, partial UPDRS-III scale for the hemibody being treated, Glass tremor scale, and PDQ8 quality of life scale were performed at baseline and during the follow-up until the final 12-month clinical visit. Neurophysiological parameters of the tremor were assessed at baseline, during the follow-up, and at the end of the 12-month follow-up after the MRg-FUS thermolesion. A video recording was made for all patients before the procedure, at the end of the MRg-FUS, and at the final evaluation during the 12-month clinical follow-up (Table 2).

Pre UPDRS III Total Mean	Pre UP-DRS III partial	Pre Glass scale	Pre PDQ8	Pre EMG Hz Rest	Pre EMG Hz Postural	Post UPDRS III Total	Post UP-DRS III Partial	Post Glass Scale	Post PDQ8 Mean	Post EMG Hz	Post EMG Hz
37,8 ± 12.2	16,5 ± 4.2	3,4 ± 0,8	24,9 ± 6.2	6,4 ± 1.2	11,1	29,5 ± 4,2 P = 0.34	8,3 ± 2.2 P = 0.022	0,3 ± 0,1 P = 0.030	11 ± 1.2 P = 0.036	1,2 ± 1 P = 0.012	0,9 ± 1 P = 0.032

Table 2: *Parkinson 'disease scales pre and post MRg-FUS. 36 months follow up.*



Picture 1: *Right ablative termo-lesion MRg-FUS in the Zona inzerta, Tractothomy (inzertothomy).*

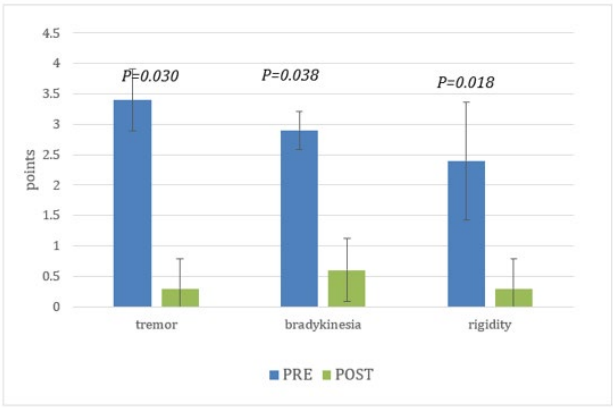
A control cranial MRI was performed on all patients to observe any potential complications and the ablative lesions (Picture 1).

Results

All 10 PD patients included in this 12-month follow-up completed the study.

At the 12-month evaluation, patients scored a mean of 0.3 points on the tremor Glass' scale, with an average improvement of 85% (from 3.4 to 0.3) (P = 0.030). They also scored a mean of 29.5 ± 4.2 (P = 0.34) points on the total UPDRS III sub-scale, with an average improvement of 21%. However, the UPDRS-III sub-scale focused on the treated hemibody scored a mean of 8.3 points, with an average improvement of 49.6% (from 16.5 to 8.3 points) (p < 0.022). The PDQ-8 quality of life scale showed a mean of 11.1 ± 1.2 points, with an improvement of 70% (Table 2).

Regarding the cardinal symptoms of PD in the treated hemibody, patients showed a mean of 0.6 points in the bradykinesia item (from 2.9 to 0.6), with an average improvement of 79.3% (P = 0.038). They also showed 0.3 points in the rigidity item, with an average improvement of 87.5% (P = 0.018), and finally, they showed 0.3 points in tremor (from 3.4 to 0.3), with an average improvement of 91% (P = 0.036) in the UPDRS III sub-scale at the 12-month evaluation (Graphic 1).



Graphic 1: *Cardinal symptoms of Parkinson disease patients, 12 months follow up pre and Post MRg-FUS.*

In terms of neurophysiological characteristics, patients showed a mean postural tremor frequency of 1.2Hz 12 months after MRg-FUS ablation (from 11.4 ± to 1.2 Hz), with an improvement of 89.4% (P = 0.012). They also showed a mean resting tremor frequency of 6.7Hz pre MRg-FUS and a mean of 0.9Hz at the final evaluation 12 months after MRg-FUS, with an improvement of 86.5% (P = 0.032) (Table 3).

PRE	Tremor Glass	Bradykinesia	Rigidity	POST	Tremor Glass	Bradykinesia	Rigidity
Mean	3,4	2,9	2,4	Mean	0,3 P=0.030	0,6 P=0.038	0,3 P=0.018

Table 3*: Cardinal symptoms of Parkinson 'disease patients in 12 months follow up.*

Discussion

Treating PD patients with tremor that is resistant to oral therapy poses a challenge for neurological groups worldwide. The widely accepted drugs for treating tremor have poor efficacy and limited benefits, with adverse effects being common. Dopaminergic therapy, such as l-dopa and Dopamine agonists, is often ineffective in improving resting and postural tremor in some PD patients, despite being successful in improving other cardinal symptoms like rigidity and bradykinesia.

While MRg-FUS has been approved by the FDA and MEA for essential tremor and tremor-predominant PD patients, there is an ongoing debate about the best target to improve all the motor and non-motor symptoms that PD patients and their caregivers experience. Extensive information exists regarding the clinical benefits of targeting the VIM and sub-thalamic nucleus for tremor and motor symptom improvement in PD patients. However, our own experience and that of other groups suggest that the VIM thalamic nucleus is successful in improving postural tremor but shows poor improvement in rigidity and bradykinesia. On the other hand, ablative lesion of the sub-thalamic nucleus can improve other cardinal symptoms of PD, but depending on the region of the Luys STN nucleus, it may only mildly improve tremor with a high risk of serious and persistent dyskinesias. Targeting the more dorsal region of the Luys STN nucleus near the Forel fields and the pallido-thalamic and sub-thalamic tracts may be a better option with a lesser risk of adverse effects. This region is also near the ZI and pallido flugal tracts, which may contribute to the excellent outcomes observed in our patients.

Despite a clear improvement in tremor and other cardinal symptoms in PD patients after MRg-FUS unilateral ablation of the STN nucleus, some authors have reported partial benefits in quality of life (QOL) scales. We believe this is because more advanced PD patients need improvement in motor fluctuations and dyskinesias, which have a greater impact on QOL. In our view, bilateral DBS of the STN luys nucleus is more effective in advanced PD patients than unilateral or bilateral ablative lesions.

Historically, PD patients with drug-resistant tremor have been treated with ablative surgical procedures like pallidotomy and Thalamotomy, followed by deep brain stimulation of the sub-thalamic nuclei of luys in advanced PD patients since 1995. Different brain targets have been proposed in the surgical treatment of PD patients with resistant tremor, including the thalamus (VIM nucleus), the Luys subthalamic nucleus (STN), the internal part of the globus pallidus (GPi), and the Pallido-thalamic tract. In our study, we performed MRg-FUS thermolesion in 10 PD patients, targeting a larger area from the most inferior area of the VIM thalamic nucleus to the Forel fields in the ZI, including the pallido-thalamic tracts passing from the GPI to the STN and the VIM-thalamic nucleus, as well as other important neurological regions of the basal ganglia.

Patients treated with MRg-FUS sub-thalamotomy who show better outcomes are likely those with lesions in the most dorsal STN area in the pallidal-STN tracts. Those with more ventral lesions show less efficacy and more adverse effects like dyskinesias.

All 10 PD patients in our follow-up study showed remarkable improvement in tremor, as reflected in the tremor glass scale (See video). They also showed clear and objective improvement in neurophysiological parameters, with significant reductions in postural and resting tremor frequencies. Additionally, there was an average improvement in the total UPDRS III sub-scale and a significant improvement in the focalized UPDRS-III sub-scale for the treated hemibody. This suggests that MRg-FUS ablative lesion provides important benefits for drug-resistant tremor in earlier stages of PD rather than in advanced PD patients.

In terms of the efficacy of MRg-FUS on other cardinal symptoms of PD in the treated hemibody, patients showed significant improvement in bradykinesia and rigidity. This improvement was also reflected in the PDQ-8 quality of life scales.

As we can see, our PD patients not only improved in terms of postural and resting tremor, but they also showed remarkable improvement in all cardinal symptoms of PD at the 12-month visit. Additionally, they experienced a significant improvement in their quality of life without any major adverse effects during the follow-up period. This significant improvement in the primary endpoints of this study can be attributed to the specific inclusion criteria of the patients in this follow-up. We observed that these patients had asymmetric parkinsonian symptoms with a prominent resistant tremor, rather than advanced PD patients with motor fluctuations and/or dyskinesias. Furthermore, the total l-dopa dose was reduced. Previous studies have shown limited improvement in advanced PD patients after ablative lesion procedures such as radiofrequency or radiotherapy.

We hypothesize that the improvement in cardinal symptoms of PD observed after MRg-FUS lesions in our patients can be explained by a thermolesion in a region just below the VIM-Thalamic nucleus, in the most rostral and ventral area of the VIM thalamic nucleus, as well as in the neighboring area corresponding to the ZI. These regions are where the pallido-flugal thalamic tracts pass from the GPI to the STN, VIM thalamic nucleus, brainstem, and other regions of the CNS, as shown in the Brain MRI of one of our PD patients (Figure 1).

According to previous publications on basal ganglia neurophysiological models in PD and short series published on PD after thalamotomies and pallidotomies by radiofrequency, the pallidal-thalamic tracts play a crucial role in rigidity and bradykinesia in PD patients [12,13].

The zona incerta (ZI) is a slip of gray matter located between the thalamic and lenticular fasciculi, which is an extension of the reticular nucleus of the thalamus. Functionally, it is divided into four parts: rostral, ventral, dorsal, and caudal. The caudal portion (cZI) is associated with motor functions and receives afferents from basal ganglia nuclei, reticular formation, and cortical regions. The rostral ZI is separated from the STN by the pallido-fugal fibers crossing the internal capsule on the dorsomedial side of the STN. The ZI receives afferent input from the GPI or substantia nigra pars reticulata (SNr), the PPN, and cortical projections. The cZI lies posterior and medial to the posterior and lateral (motor) portion of the STN and has also been used as a target for DBS. We believe that after lesioning the cZI in our PD patients, they not only showed significant improvement in postural, action, and resting tremor, but also in other cardinal features of PD such as bradykinesia and rigidity. This improvement is reflected in their quality of life, as shown in the results.

MRg-FUS has proven to be quite effective in essential tremor patients when the VIM thalamic nucleus is lesioned. However, the rationale for using MRg-FUS in PD patients with a drug-resistant tremor is different because other cardinal symptoms of Parkinson's disease, such as rigidity and bradykinesia, can improve better when different targets are chosen. The STN nucleus of luys has been reported as a good target for MRg-FUS to alleviate symptoms in PD patients, including tremor. However, there is a well-known potential risk of severe and disabling dyskinesias when the STN lesion extends to the more ventral and anterior region of the STN. On the other hand, a smaller lesion of the STN to avoid undesirable dyskinesia can limit the long-lasting effect of this therapy.

As demonstrated in this follow-up, MRg-FUS in the VIM and neighboring areas of the ZI is a very promising technique that provides essential advantages and few adverse effects compared to other brain targets for Parkinson's disease patients with tremor resistance. It

is a less invasive procedure compared to other surgical interventions that require opening the skull and introducing electrodes into the brain for deep brain stimulation or radiofrequency thermocoagulation.

Conclusion

The PD patients with predominant tremor improved cardinal parkinsonian symptoms after thermolesion in the pallidal-thalamic tracts in the ventral area of the VIM thalamic nucleus and in the zona incerta of the Foreld fields with MRg-FUS during this 12-month follow-up. These patients experienced improvements in resting, postural, and action tremors, as well as bradykinesia and rigidity in the treated hemi-body. This improvement was also reflected in the quality of life of these PD patients observed for at least 12 months after the MRg-FUS tractotomy.

The inactivation of the pallido-flugal tracts, which pass from the GpI to the Stn, VIM, and the brainstem, is likely directly related to the improvement of all the parkinsonian symptoms in our PD patients, not just the tremor as typically seen with lesions exclusively in the VIM thalamic nucleus. Our patients showed persistent improvement without adverse effects and the mean l-dopa dose was reduced and remained stable for at least 12 months. Better-designed studies, including longer follow-ups, should be conducted to confirm our findings. Nevertheless, the low rate of adverse effects and the positive clinical outcomes observed in this 12-month follow-up provide evidence to consider the most rostral area of the thalamic VIM nucleus and the nonboring area of the ZI as a good choice target for improving the cardinal symptoms of PD and the quality of life for PD patients with predominant tremor.

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