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Magnetic resonance–guided focused ultrasound thalamotomy for tremor: a report of 30 Parkinson's disease and essential tremor cases

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OBJECTIVE Thalamotomy of the ventral intermediate nucleus (VIM) is effective in alleviating medication-resistant tremor in patients with essential tremor (ET) and Parkinson's disease (PD). MR-guided focused ultrasound (MRgFUS) is an innovative technology that enables noninvasive thalamotomy via thermal ablation.

METHODS Patients with severe medication-resistant tremor underwent unilateral VIM thalamotomy using MRgFUS. Effects on tremor were evaluated using the Clinical Rating Scale for Tremor (CRST) in patients with ET and by the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS) in patients with PD and ET-PD (defined as patients with ET who developed PD many years later). Quality of life in ET was measured by the Quality of Life in Essential Tremor (QUEST) questionnaire and in PD by the PD Questionnaire (PDQ-39).

RESULTS Thirty patients underwent MRgFUS, including 18 with ET, 9 with PD, and 3 with ET-PD. The mean age of the study population was 68.9 ± 8.3 years (range 46–87 years) with a mean disease duration of 12.1 ± 8.9 years (range 2–30 years). MRgFUS created a lesion at the planned target in all patients, resulting in cessation of tremor in the treated hand immediately following treatment. At 1 month posttreatment, the mean CRST score of the patients with ET decreased from 40.7 ± 11.6 to 9.3 ± 7.1 ($p < 0.001$) and was 8.2 ± 5.0 six months after treatment ($p < 0.001$, compared with baseline). Average QUEST scores decreased from 44.8 ± 12.9 to 13.1 ± 13.2 ($p < 0.001$) and was 12.3 ± 7.2 six months after treatment ($p < 0.001$). In patients with PD, the mean score of the motor part of the UPDRS decreased from 24.9 ± 8.0 to 16.4 ± 11.1 ($p = 0.042$) at 1 month and was 13.4 ± 9.2 six months after treatment ($p = 0.009$, compared with baseline). The mean PDQ-39 score decreased from 38.6 ± 16.8 to 26.1 ± 7.2 ($p = 0.036$) and was 20.6 ± 8.8 six months after treatment ($p = 0.008$). During follow-up of 6–24 months (mean 11.5 ± 7.2 months, median 12.0 months), tremor reappeared in 6 of the patients (2 with ET, 2 with PD, and 2 with ET-PD), to a lesser degree than before the procedure in 5. Adverse events that transiently occurred during sonication included headache (n = 11), short-lasting vertigo (n = 14) and dizziness (n = 4), nausea (n = 3), burning scalp sensation (n = 3), vomiting (n = 2) and lip paresthesia (n = 2). Adverse events that lasted after the procedure included gait ataxia (n = 5), unsteady feeling (n = 4), taste disturbances (n = 4), asthenia (n = 4), and hand ataxia (n = 3). No adverse event lasted beyond 3 months. Patients underwent on average 21.0 ± 6.9 sonications (range 14–45 sonications) with an average maximal sonication time of 16.0 ± 3.0 seconds (range 13–24 seconds). The mean maximal energy reached was 12,500 ± 4274 J (range 5850–23,040 J) with a mean maximal temperature of 56.5° ± 2.2°C (range 55°–60°C).

CONCLUSIONS MRgFUS VIM thalamotomy to relieve medication-resistant tremor was safe and effective in patients with ET, PD, and ET-PD. Current results emphasize the superior adverse events profile of MRgFUS over other surgical approaches for treating tremor with similar efficacy. Large randomized studies are needed to assess prolonged efficacy and safety.

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KEY WORDS MR-guided focused ultrasound; essential tremor; thalamotomy; Parkinson's disease; treatment; functional neurosurgery

ABBREVIATIONS AC-PC = anterior commissure-posterior commissure; CRST = Clinical Rating Scale for Tremor; DBS = deep brain stimulation; ET = essential tremor; MRgFUS = MR-guided focused ultrasound; PD = Parkinson's disease; PDQ-39 = PD Questionnaire; QUEST = Quality of Life in Essential Tremor; RF = radiofrequency; UPDRS = Unified Parkinson's Disease Rating Scale; VIM = ventral intermediate nucleus.

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Tremor is the dominant symptom of essential tremor (ET) and a common symptom of Parkinson's disease (PD). Tremor hampers activities of daily living and causes social embarrassment and isolation. Tremor can be medically treated but medications have unpredictable effects on tremor and harbor an increased risk of adverse effects.[9,18,24] Surgical treatment options for patients with medication-resistant tremor include deep brain stimulation (DBS), radiofrequency (RF) thalamotomy, and radiation thalamotomy. Some of these surgical procedures have been known since the last half of the 20th century.[27,29] These surgical treatments target specific neuroanatomical areas. The ventral intermediate nucleus (VIM) is the preferred target for patients with ET and for some patients with tremor-predominant PD.[2,27]

Currently, the most popular surgical procedure for tremor abatement for these disorders is DBS, which is effective in reducing tremor in most patients. DBS consists of placing electrodes through a bur hole in the skull and electrically stimulating the VIM in patients with ET, and the subthalamic nucleus, globus pallidus internus, and VIM in patients with PD. Electrode stimulation is generated by an implantable neurostimulator. The major advantage of DBS is its reversibility and the possibility to individually tailor stimulator adjustments to achieve optimal tremor control. The drawbacks are the high complication rates due to misplacement of the electrode leads, hardware failure, systemic bacterial infections of the leads, rare intracranial bleeding, and seizures. A recent report of adverse events of DBS in more than 600 patients with ET disclosed a complication rate of 7.1%, mostly hemorrhage, infection, dysarthria, and disequilibrium.[8] Another report of DBS in patients with PD with early motor complications showed a 17.7% serious adverse event rate related to surgical implantation.[25] DBS also requires frequent follow-up and programming that are uncomfortable for the patients and time consuming for both medical staff and patients. Therefore, DBS failure may result from suboptimal programming and inadequate access to care.[12] Furthermore, the DBS procedure is costly and requires periodic battery replacement. Even without these drawbacks associated with DBS, many patients are reluctant to undergo bur hole drilling followed by invasive cranial surgery and intracranial electrode implantation.

Another surgical option is thalamotomy. This procedure has been known for decades as beneficial in alleviating tremor in patients with severe medication-refractory tremor.[20] It can be performed using RF or Gamma Knife ionizing radiation. Unilateral thalamotomy using RF has been reported effective in 73%–93% of patients but is accompanied by permanent complications in 9%–23%.[10] Bilateral thalamotomy using RF carries an even a higher risk of complications including anarthria and dysphagia, and therefore it is rarely performed today.[26] Thalamotomy using the Gamma Knife is effective but the beneficial clinical effects are delayed and prevent accurate localization and size determination of the planned lesion.[14] With Gamma Knife thalamotomy there is an added risk of delayed serious adverse events secondary to ionizing radiation such as radiation necrosis[21] and collateral trajectory tissue damage.[31]

Magnetic resonance–guided focused ultrasound (MRgFUS) is a new technology that uses ultrasound energy for focal thermal ablation.[1,4,6,11,15,23] With this technique, the MRI serves as the surgeon's eyes for targeting the energy and the ultrasound rays serve as the surgeon's knife for creating the lesion. These rays heat the tissue, thereby causing thalamotomy because heating any tissue (normal or abnormal) to 56°C for 1 second denatures protein, thus causing 100% cell death. A combination of tissue temperature and length of exposure to this heat defines the extent of the lesion. By focusing the heat on more than 1 point or by scanning the focus, a volume of tissue can be thermally ablated. A subset of patients has a skull density that does not allow sufficient heating of intracranial structures. This can usually be foreseen by calculating skull density ratio before treatment is attempted.[5]

MRgFUS surgery is performed in the MRI suite. The MRI machine is used for target definition, treatment planning, and intervention guidance with high precision. Simultaneous real-time monitoring of the temperature at the target is achieved with MR thermometry,[19] allowing for a gradual procedure that enables monitoring of the degree of heating at the target during sonication. At low temperatures, the effects of which are presumed to be reversible, clinical monitoring enables target repositioning according to possible reported adverse effects, if any. Definitive nonreversible thermal ablation is performed only after temporary tremor reduction when the patient reports no adverse effect. This is a new technology and therefore there is limited experience compared with other techniques. Using this staged procedure approach, adverse events reported included paresthesias, dysesthesia, and deep vein thrombosis in a small number of patients.[4,6,11,16,23,30] The preferred target for hand tremor is currently the VIM. This procedure can also potentially treat leg and head tremors that sometimes accompany the hand tremor by taking into consideration the somatotopic organization within the VIM. MRgFUS carries no risk for infection and hardware failure, and postoperative programming is not needed as the effect is achieved immediately at the end of the procedure. Because the procedure does not involve any kind of brain penetration and does not have the complications associated with ionized radiation or foreign object implantation, patients are less reluctant to undergo this procedure in comparison with DBS and other thalamotomy techniques (although some remain reluctant, especially women, because of the need to shave one's head). A unique possible complication of the procedure is cavitation. One patient treated for neuropathic pain suffered a thalamic hemorrhage with motor deficits related to cavitation, presumably caused by increasing the target temperature to 64°C.[14] Following this severe adverse event, an alert of cavitation was installed in the MRgFUS system that aborts sonications that may cause this complication. MRgFUS treatment has been approved in Europe and Israel for treating tremor. In this paper we report our experience using MRgFUS VIM thalamotomy in 30 patients suffering from medication-resistant tremor due to PD, ET, or ET-PD.

Methods

Patient Population

Thirty patients with severe refractory tremor underwent MRgFUS thalamotomy, using a focused ultrasound sys-

TABLE 1. Patient characteristics

Case No.	Age (yrs), Sex	Diagnosis	Duration of Tremor (yrs)	Dominant Hand	Treated Hand	FU (mos)
1	73, M	ET	14	Rt	Rt	24
2	79, F	ET	30	Rt	Rt	24
3	61, M	PD	10	Rt	Rt	24
4	66, M	PD	7	Rt	Rt	24
5	70, M	ET	5	Rt	Rt	24
6	67, M	ET	30	Rt	Lt	12
7	65, M	PD	7	Rt	Rt	12
8	51, M	PD	2	Rt	Lt	14
9	75, F	ET	25	Rt	Rt	18
10	78, M	ET	20	Lt	Lt	18
11	74, M	ET	24	Rt	Rt	18
12	77, M	ET	10	Rt	Rt	3
13	74, F	PD	4	Rt	Rt	12
14	57, M	PD	3	Lt	Lt	3
15	78, F	ET	5.5	Lt	Rt	12
16	67, M	ET	30	Rt	Rt	12
17	69, F	ET	5	Lt	Lt	12
18	46, M	PD	2.5	Rt	Rt	12
19	59, M	PD	10	Lt	Lt	1
20	64, M	ET	15	Rt	Rt	12
21	75, M	ET-PD	15	Rt	Rt	3
22	66, F	ET	15	Lt	Lt	6
23	70, M	ET-PD	16	Rt	Rt	6
24	66, M	ET	20	Rt	Rt	6
25	69, M	ET	10	Rt	Rt	6
26	77, F	ET	7	Rt	Rt	6
27	73, M	ET-PD	5	Rt	Rt	6
28	79, M	ET	5	Rt	Rt	6
29	87, M	ET	8	Rt	Rt	6
30	56, M	PD	2	Rt	Lt	3

FU = follow-up.

tem (650-kHz system, ExAblate, Insightec) for VIM ablation (Table 1). VIM thalamotomy was performed contralateral to the patient's hand preference. All patients were offered either DBS or MRgFUS and preferred MRgFUS as their treatment of choice. The diagnosis of ET and tremor-dominant PD was confirmed by a neurologist specializing in movement disorders according to accepted criteria.[13] Refractory tremor was considered a disabling tremor after ample treatment trials. For ET, a clinically significant tremor was defined as a score of more than 2 on the postural or action item on the Clinical Rating Scale for Tremor (CRST; range 0–4), as well as substantial disability in the performance of at least 2 daily activities from the disability subsection of the scale. For PD and ET-PD, tremor was measured by the motor part of the Unified PD Rating Scale (UPDRS)[7] in the ON stage. A score of more than 3 (range 0–4) on either item 20 or 21 of the UPDRS was defined as a severe disabling tremor. ET-PD was diagnosed in patients with long-standing ET who developed PD symptoms many years later.[28]

All patients had no contraindications for the procedure including, but not limited to, significant cognitive decline, current anticoagulant or anti-aggregant therapy, brain tumors, vascular malformations, significant unstable medical conditions, and contraindications for MRI, including claustrophobia.

Assessments

Tremor scores were assessed as detailed above. Quality of life in patients with ET was measured by the Quality of Life in Essential Tremor (QUEST) questionnaire and in patients with PD and ET-PD by the PD questionnaire (PDQ-39). Assessment after the procedure was usually performed 1 day, 1 week, 1–3 months, 6 months, and 1 year after treatment and was repeated yearly.

Pretreatment Imaging

All patients underwent preprocedural MRI and CT. All MRI studies were performed using a 3-T system (MR750,

GE) and included high-resolution T2-weighted fast spin echo scans on the sagittal, axial, and coronal planes as well as routine sequences for evaluation of brain structures. A head CT scan was obtained (1-mm consecutive slices, 350 mAs, and FOV of 254 mm) with no tilt and reconstructed with 3 different bone kernels. CT images were used to assess ultrasound penetration by calculating the ratio between the bone and the bone marrow of the skull (skull density ratio), in which a ratio of 0.3 or greater was considered suitable for treatment.

Treatment Planning

Fusion of MRI images and preoperative CT was performed on an ExAblate Neuro console, and calcifications and air-containing structures (such as the frontal sinuses) marked were defined as no-pass areas for the ultrasound rays. Planning was conducted on an axial MRI plane passing through the anterior and posterior commissures (AC-PC line) to determine the dorsoventral zero plane. The initial target coordinates for the VIM were calculated to be located at 25% of the AC-PC distance anterior to the PC and 14 mm lateral to the AC-PC line. When there was third ventricle enlargement, the initial target was 11.5 mm lateral to the third ventricle wall.

Pre-thalamotomy Procedure

On the day of treatment, the patient's head was shaved completely leaving no stubble to avoid any air bubble interrupting the ultrasound penetration. After administering local anesthesia containing a mixture of 2% lidocaine and 0.5% marcaine, a stereotactic frame crown (CRW Integra) was fixed with screws to the skull to achieve head fixation to the MRI table. An elastic silicone diaphragm was then adapted to the patient's head and affixed after applying EMLA cream (lidocaine/prilocaine) 30 minutes prior to the treatment procedure. The patient's head with the diaphragm was attached to the focused ultrasound helmet (with 1024 transducers) affixed to a specifically designed MRI bed. The space between the helmet and the diaphragm was filled with degassed circulating cold water. After positioning of the patient in the MRI scanner, a T2-weighted MRI scan was performed in the sagittal, axial, and coronal planes for real-time planning as well as reassessment and comparison with the preoperative planning. The target coordinates were redefined and MRI central frequency was measured. Afterward, the transducer's focal point was mechanically adjusted to no more than 0.5 mm from the target in the x, y, and z planes. The patient held an emergency stop button and stayed awake and cooperative throughout the procedure. All patients wore elastic stockings to prevent vein thrombosis.

Thalamotomy Using MRgFUS

MRgFUS sonication was performed using 3-T MRI and an ExAblate Neuro focused ultrasound system. The procedure was performed in 3 stages. The first stage included sonications at very low energy to confirm that the sonication was in the selected target in 3 planes (sagittal, axial, and coronal). When needed, the sonication focus was adjusted. The temperature at this stage typically reached 41°–46°C. The second stage involved sonication at gradually increasing energy to achieve a temporary effect on tremor and to confirm the absence of adverse effects. The target was continuously examined for accuracy according to the planned coordinates and to the patient's clinical and neurological examination, including tremor evaluation by drawing spirals, writing, cup holding, and other preoperative known tremor-triggering maneuvers. The coordinates were repositioned when necessary according to the clinical status and adverse effects, if any. When no amelioration of tremor was observed, the sonication focus was moved until tremor reduction was achieved, taking into account the anatomy of the VIM somatotopic arrangement and its thalamic surrounding nuclei. Typically, temperature at this stage reached 46°–50°C. The third stage, the ablation stage, included a gradual increase in total energy by either increasing intensity of sonication or by prolonging the duration of sonication. Sonications were stopped when adequate control of tremor was achieved, with the temperature reaching no more than 60°C.

Immediately after treatment completion and removal of the stereotactic frame, a T2- and diffusion-weighted MRI scan was obtained to ensure lesion formation and to exclude radiologically visible complications.

Statistical Analysis

Total tremor severity scores before and after the procedure were compared using a paired t-test and were considered significantly different for p values < 0.05. Quality of life scores for ET were compared separately from those of patients with PD and ET-PD, which were grouped together, using a paired t-test and were considered significantly different for p values < 0.05.

Results

Patient Characteristics

Between November 2013 and January 2016, 18 patients with ET, 9 with PD, and 3 with ET-PD underwent unilateral MRgFUS VIM thalamotomy at the Rambam Health Care Campus in Haifa, Israel. All patients had medication-resistant tremor. Twenty-four patients were right-handed. Tremor was more prominent on the right side in 22 of the patients. The mean age of patients (± SD) was 68.9 ± 8.3 years (range 46–87 years) with mean disease duration of 12.1 ± 8.9 years (range 2–30 years). Baseline demographics and clinical features of the study population are listed in Table 1. Five patients received levodopa, 4 with PD and 1 with ET-PD. Patients with PD on levodopa suffered from motor fluctuations, whereas the patient with ET-PD did not. Follow-up duration was 6–24 months (mean 11.5 ± 7.2 months, median 12.0 months) with few patients not completing all follow-up visits (Tables 2–4).

Tremor

Hand tremor was abolished immediately following the procedure in all 30 patients. In 3 patients, an accompanying leg tremor was also abolished and in 2 other patients an accompanying head tremor was abolished as well. The mean CRST scores of the patients with ET decreased from 40.7 ± 11.6 to 9.3 ± 7.1 ($p < 0.001$) 1 month after

TABLE 2. Tremor and quality of life scores in patients with ET before and after MRgFUS

Case No.	CRST Score			QUEST Score		
	Before	After 1 Mo	After 6 Mos	Before	After 1 Mo	After 6 Mos
1	53	9	4	41	1	1
2	48	6	6	37	0	4
5	58	19	6	42	0	20
6	42	6	7	50	16	17
9	45	18	12	72	50	15
10	58	16	5	29	15	5
11	39	5	9	40	4	4
12	24	2	6	39	1	23
15	42	5	8	60	0	12
16	46	6	4	42	10	22
17	50	9	4	71	28	6
20	45	24	17	39	25	14
22	24	7	7	43	15	20
24	29	1	9	43	34	22
25	41	5	11	50	7	2
26	23	21	22	36	11	12
28	43	2	4	51	13	15
29	23	6	6	21	6	8
Mean ± SD	40.7 ± 11.6	9.3 ± 7.1	8.2 ± 5.0	44.8 ± 12.9	13.1 ± 13.2	12.3 ± 7.2
p Value		<0.001	<0.001		<0.001	<0.001

treatment and was 8.2 ± 5.0 six months after treatment ($p < 0.001$, compared with baseline; Table 2). In patients with PD, the mean motor UPDRS score at baseline was 24.9 ± 8.0 points and decreased to a mean of 16.4 ± 11.1 points ($p = 0.04$) at 1 month and was 13.4 ± 9.2 six months after treatment ($p = 0.009$, compared with baseline; Table 3). At 1 month, item 20 and item 21 of the UPDRS decreased from 2.90 ± 0.99 to 0.40 ± 0.97 ($p < 0.001$) and from 3.00 ± 1.16 to 0.60 ± 0.97 ($p < 0.001$), respectively, and at 6 months to 0.3 ± 0.5 and 0.6 ± 1.1, respectively. In patients with ET-PD, the mean UPDRS score decreased from 34.7 ± 7.1 to 22.7 ± 7.5 at 1 month and to 17.1 ± 7.1 at 6 months (Table 4). Statistical analysis was not conducted in this group due to the small number of patients.

Twenty-four patients (80% of the patients) experienced sustained tremor relief. Six patients—2 with ET (11% of ET patients), 2 with PD (22% of PD patients), and 2 with ET-PD (67% of patients with ET-PD)—suffered some tremor recurrence during the first 6 months following the procedure (mean 2.5 months, median 2 months). The tremor that recurred was significantly less disabling than before the procedure in all but 1 patient with ET-PD. In

TABLE 3. Tremor and quality of life scores in patients with PD before and after MRgFUS

Case No.	UPDRS Motor Score			PDQ-39 Score		
	Before	After 1 Mo	After 6 Mos	Before	After 1 Mo	After 6 Mos
3	34	32	4	41	31	17
4	23	33	31	41	31	12
7	22	10	8	62	30	19
8	21	8	19	17	—	33
13	32	21	14	45	37	35
14	18	11	11	32	21	21
18	39	23	7	63	23	15
19	18	7	—	29	21	—
30	17	3	—	17	15	13
Mean ± SD	24.9 ± 8.0	16.4 ± 11.1	13.4 ± 9.2	38.6 ± 16.8	26.1 ± 7.2	20.6 ± 8.8
p Value		0.042	0.009		0.036	0.008

TABLE 4. Tremor and quality of life scores in patients with ET-PD before and after MRgFUS

Case No.	UPDRS Motor Score			PDQ-39 Score		
	Before	After 1 Mo	After 6 Mos	Before	After 1 Mo	After 6 Mos
1	41	27	—	—	—	—
2	27	14	22	24	7	14
3	36	27	12	25	6	1

all but 1 patient, the tremor that recurred was significantly less disabling than before the procedure. In 1 patient with ET, tremor recurred after 3 weeks but was less debilitating than before the procedure. In the other patient with ET, tremor precluded all activities before the procedure, but when it recurred 3 months after the treatment, it was only when writing. In the patients with PD, recurrent significant tremor occurred after 3 months in 1 patient, but to a lesser degree than before the procedure, while minimal tremor appeared in another patient after 6 months. In the 2 patients with ET-PD, tremor reappeared after 1 month, to the same extent as before the treatment in 1 patient and to a lesser degree in the other patient. No patient has so far showed recurrence of tremor after 6 months.

Quality of Life and Other Questionnaires

Quality of life scores were improved in 29 of the 30 patients 1 month following the procedure. In patients with ET, quality of life evaluations using the QUEST questionnaire decreased significantly from 44.8 ± 12.9 before the procedure to 13.1 ± 13.2 one month after the procedure ($p < 0.001$) and was 12.3 ± 7.2 at 6 months ($p < 0.001$, compared with baseline; Table 2). In patients with PD, the PDQ-39 quality of life measure decreased from 38.6 ± 16.8 before the procedure to 26.1 ± 7.2 one month after the procedure ($p = 0.036$), and was 20.6 ± 8.8 at 6 months ($p = 0.008$, compared with baseline; Table 3). The improvement in quality of life was sustained in 94% of the patients with ET, 78% of the patients with PD, and 66% of the patients with ET-PD (Tables 2–4). Clinical assessment by the examiner and patients changed from severe disability to no functional disability immediately following the procedure in all patients. Twenty-nine of 30 patients reported subjective satisfaction from the procedure during follow-up.

Adverse Events

Table 5 summarizes the adverse events during the procedure as well as postoperatively. Most adverse events occurred only during the sonication sessions and included short-lasting vertigo (n = 14), short duration sharp headache (n = 11), dizziness (n = 4), nausea (n = 3), burning skull sensation (n = 3), and vomiting (n = 2). Lip paresthesias (n = 2) did not recur after relocating the target 1 mm anterior to the original target coordinates. Adverse events that lasted after the procedure were mainly due to unsteady gait. Five patients (3 with ET, 1 with PD, and 1 with ET-PD) showed postoperative gait ataxia, 4 had asthenia, and 3 experienced hand ataxia as well (2 with ET, 1 with ET-PD). These patients had preoperative clinical signs of unsteady gait when walking tandem. In these patients, significant edema around the lesion was noted and therefore they were given 8–12 mg of oral dexamethasone per day for 1 week. In all patients, gait abnormality, hand ataxia, and asthenia were transient and gradually resolved (Table 5). Four patients had no objective new neurological signs, specifically no ataxia, upon examination. In these patients, this complaint resolved within 4 weeks. Mild dysgeusia of up to 3 months was reported by 4 patients. Adverse events related to the stereotactic frame positioning were scalp numbness (n = 5) and small subcutaneous hematoma in the frontal area due to the frame screws (n = 3), both of which resolved within 1–4 weeks.

TABLE 5. Adverse events

Adverse Event	No. of Patients	Time to Resolution
Related to sonication		
Vertigo	14	Secs
Headache	11	Secs to mins
Dizziness	4	Secs to mins
Nausea	3	Mins
Burning scalp sensation	3	Secs
Vomiting	2	Mins
Lip paresthesia	2	Secs
Related to thalamotomy		
Gait ataxia	5	1–3 mos
Unsteady feeling	4	1–4 wks
Taste disturbance	4	1–3 mos
Asthenia	4	1–4 wks
Hand ataxia	3	1–4 wks
Related to stereotactic frame		
Scalp numbness	5	1–4 wks
Hematoma near the eye	3	1–2 wks

Sonication Measures

All patients' skull density ratio was suitable for treatment. During sonication we increased the energy in a stepwise fashion until 1 of the following occurred: 1) adequate tremor control, 2) temperature reached 60°C, or 3) adverse events were unbearable. Patients underwent on average 21.0 ± 6.9 sonications (range 14–45 sonications) with an average maximal sonication time of 16.0 ± 3.0 seconds (range 13–24 seconds; Table 6). The maximal energy reached was on average 12,500 ± 4274 J (range 5850–23,040 J) with averaged maximal temperature of 56.5° ± 2.2°C (range 55°–60°C; Table 6).

Radiological Assessment

Posttreatment imaging was obtained immediately following treatment, 1 day after the procedure, after 1 week, after 1–3 months, and then yearly after treatment in most patients. The MRgFUS resulted in close to a spherical lesion in the planned target with a diameter of 4–9 mm

TABLE 6. Sonication measures

Case No.	Max Energy (J)	Max Temp (°C)	Max Sonication Time (sec)	No. of Sonications
1	11,050	58	17	14
2	7,800	57	13	18
3	13,600	55	17	21
4	23,040	55	20	17
5	15,500	51	16	20
6	9,600	59	16	21
7	7,800	58	13	21
8	5,850	58	17	17
9	16,560	59	20	24
10	13,000	59	17	23
11	12,971	58	17	20
12	9,100	60	13	16
13	8,050	59	13	15
14	20,985	55	24	24
15	12,800	57	17	17
16	7,800	60	13	14
17	10,822	56	13	15
18	19,337	55	17	45
19	17,270	55	17	25
20	14,578	58	17	36
21	9,412	55	13	16
22	9,971	56	13	24
23	8,840	55	13	15
24	13,923	52	13	30
25	15,120	58	21	32
26	11,067	56	17	16
27	9,458	57	13	18
28	19,320	54	21	20
29	9,185	56	13	16
30	11,195	55	17	21

Max = maximal; temp = temperature.

(mean 6.8 ± 1.5 mm; Fig. 1A) surrounded by mild edema on Day 1 after the procedure, with increased edema 1 week after the procedure. The edema lasted for 3–5 weeks following the procedure. At 3 months, the lesion decreased in size and the edema resolved (Fig. 1B), and at 1-year follow-up, the lesion was sometimes difficult to identify (Fig. 1C), with no correlation of the residual lesion size to the sustained tremor relief. MRgFUS resulted in a lesion at the planned target. In a scan performed 2–3 months after the procedure, the lesions markedly decreased in size.

Discussion

We report our results in 30 patients with medication-resistant tremor, including 18 patients with ET, 9 with PD, and 3 with ET-PD. Tremor was abolished in all patients immediately following the procedure. Adverse effects were mostly mild and all were transient. All patients reported improvement in quality of life immediately after the procedure. The effect of MRgFUS on tremor was stable over time in most patients (n = 24), with tremor recurring in 6 patients within the first 6 months. No patient reported tremor recurrence after the 6-month follow-up visit. Patients with ET had the highest probability to remain tremor free after the procedure (89%) in comparison with patients with PD (78%) and patients with ET-PD (33%). When tremor returned it was to a lesser extent than before the procedure in all but 1 patient. Over time, all but this 1 patient reported improved quality of life. Currently, VIM DBS is considered the treatment of choice for medication-refractory patients with disabling tremor. Our results of tremor reduction are comparable to those reported with unilateral VIM DBS. The overall effect of VIM DBS in ET is approximately 90% tremor reduction with a follow-up period of 1–2 years,[16] whereas in our experience with MRgFUS tremor reduction was noted in 100% of patients immediately following the procedure. Eighty-nine percent of patients with ET were tremor free throughout the length of our follow-up period. Similarly, the effect of VIM DBS in PD has been reported as 82%–86% tremor reduction contralateral to the lesion.[22] Our results with VIM MRgFUS show complete tremor reduction immediately following the procedure in all patients with tremor recurrence in 2 of the 9 patients with PD. Thus, the overall long-term effect of freedom from tremor in patients with PD was 78% in our patients, modestly worse than DBS results. The tremor that recurred was less severe than before the procedure in all patients. In patients with ET-PD, we did not find reports of surgical outcomes. In this unique group, the result of MRgFUS was less favorable, with return of tremor in 2 of the 3 patients within 1 month, albeit larger numbers are required to draw meaningful conclusions.

One of the major differences between MRgFUS treatment and DBS was in the adverse events profile. While our patients suffered only mild transient adverse events, the complication prevalence rate of DBS from a database of more than 600 patients with ET was 7.1%, and was even higher from a recent study of patients with PD.[8,26]

Invasive RF thalamotomy has comparable efficacy to MRgFUS and DBS, with relief of tremor cited as up to 90%. The major difference between this procedure and MRgFUS treatment is again in the adverse event profile. While as stated above, our patients experienced only mild and transient adverse events, the adverse events reported after invasive RF included intracerebral or extracerebral hemorrhage, seizures, infection, brain displacement, tension pneumocephalus, and direct injury from probe placement.[10]

Gamma Knife thalamotomy is reported to achieve approximately 90% tremor relief as well,[3,31] but as opposed to the other procedures mentioned above in which tremor relief is noted immediately or a short time after the procedure, with Gamma Knife thalamotomy there is a long lag to the beginning of tremor relief that appears only approximately 1 year following radiation.[31] A recent review indicated that the most common adverse events after Gamma Knife thalamotomy include motor complications ranging from mild transient weakness to permanent hemiparesis and dysphagia.[3,21] Alarmingly, 3 different groups reported

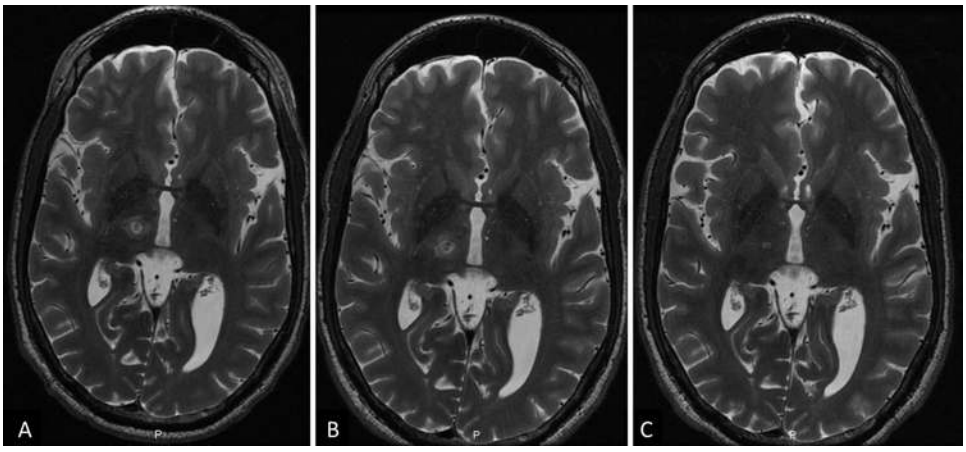

FIG. 1. Axial T2-weighted MR images. The slice of the target is presented at 3 time points: 1 day after the procedure (**A**), 1 week after the procedure (**B**), and 2 months after the procedure (**C**). Lesion size and surrounding edema slightly increased on the 1-week postprocedural scan. On the 2-month postprocedural scan, all lesions had decreased in size and the edema surrounding the lesion in the first week had resolved.

patient deaths attributed to the Gamma Knife thalamotomy.[3]

There are few previous reports of MRgFUS VIM thalamotomy. Three previous reports showed favorable results in patients with ET using MRgFUS unilateral VIM thalamotomy. Lipsman et al. were the first to report their experience of using MRgFUS for thalamotomy.[17] They described immediate and sustained improvement of tremor over 90 days in 4 treated patients. The adverse events reported in that study after sonication included paresthesias that persisted at 3 months in 1 patient and deep vein thrombosis in another. Elias et al. reported their pilot study results in 15 patients with ET.[6] They showed that tremor significantly improved in the contralateral hand. A beneficial effect on axial tremor was noted in 6 of 10 patients and on vocal tremor in 5 of 9 patients. Adverse effects after sonication included long-lasting paresthesias of the lips and tongue in 9 patients that persisted in 2 of them. One of these patients had finger dysesthesia in the index finger, which was categorized by the clinical team as a serious adverse event. Five of their patients reported temporary unsteadiness without objective change on neurological examination, while 4 other patients had objective decline in the dynamic gait index and were classified as having ataxia at 1 week following the procedure with complete resolution before the 1-month follow-up visit. Other adverse events included weak grip for 5 days in 1 patient and slurred speech for 1 day in another. Chang et al. reported treating 8 patients with ET.[4] Among these patients, 1 suffered a delayed postoperative transient balance problem that was relieved after oral steroid therapy. The treated patients showed an immediate and sustained improvement in tremor during a 6-month follow-up period. Interestingly, they were unable to achieve sufficient temperatures in 3 other patients, maybe due to their skull density ratio. Our results of relief in arm tremor in patients with ET were similar to those previously reported with MRgFUS.[4,6,17,23,30] We were also able to relieve leg tremor in 3 patients and head tremor in 2 patients when they were present by deliberately directing the ultrasound focus to these regions.

Our adverse event profile was similar to the other MRgFUS studies reported. All the adverse events that we reported were transient. Adverse events that occurred after MRgFUS were observed in patients with significant edema around the lesion and were relieved with oral steroids. We noted that patients who had documented unsteadiness prior to the procedure were more prone to suffer unsteadiness amplification after the procedure. One adverse event that was not previously reported is change in the taste quality during eating on the treated side. This symptom was observed in 13% of the patients and lasted for 1–3 months. Taste examination did not show an objective taste deficit. This unique complaint may be due to the effect of treatment on the gustatory area in the ventral posterior complex of the thalamus or to a smell-related phenomena. No intracranial hemorrhage or postoperative seizures were encountered in our cohort of 30 patients and there were no trajectory-related complications.

In our patients we achieved complete resolution of the tremor in a relatively wide range of treatment temperatures, energy parameters, number of sonications, sonication durations, and lesion sizes. We found no correlations between treatment success and effect sustainability and these parameters.

Conclusions

MRgFUS is a novel treatment for tremor. The procedure is noninvasive, uses real-time MRI for morphological and thermal monitoring, and there is no need for anesthesia or a sterile operating room. It is effective and immediate results are obtained without major adverse events. The ability to accurately target different specific regions in the VIM thalamus according to the somatotopic arrangement, thus sculpting the lesion with immediate relief of tremor in different body regions during a single procedure, is unique to this technology. There is no need for hardware adjustment and it is very appealing for patients who usually hesitate to be treated by invasive surgery for tremor, even when it causes a marked reduction in quality of life. Our results need to be verified by larger studies with longer follow-up times to evaluate its long-term safety and efficacy.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Zaaroor, Sinai, Goldsher, Eran, Schlesinger. Acquisition of data: Sinai, Schlesinger. Analysis and interpretation of data: Zaaroor, Sinai, Goldsher, Eran, Schlesinger. Drafting the article: Zaaroor, Sinai, Schlesinger. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Zaaroor. Statistical analysis: Sinai.

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