MR-guided focused ultrasound thalamotomy for essential tremor: a proof-of-concept study

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Summary

Background Essential tremor is the most common movement disorder and is often refractory to medical treatment. Surgical therapies, using lesioning and deep brain stimulation in the thalamus, have been used to treat essential tremor that is disabling and resistant to medication. Although often effective, these treatments have risks associated with an open neurosurgical procedure. MR-guided focused ultrasound has been developed as a non-invasive means of generating precisely placed focal lesions. We examined its application to the management of essential tremor.

Methods Our study was done in Toronto, Canada, between May, 2012, and January, 2013. Four patients with chronic and medication-resistant essential tremor were treated with MR-guided focused ultrasound to ablate tremor-mediating areas of the thalamus. Patients underwent tremor evaluation and neuroimaging at baseline and 1 month and 3 months after surgery. Outcome measures included tremor severity in the treated arm, as measured by the clinical rating scale for tremor, and treatment-related adverse events.

Findings Patients showed immediate and sustained improvements in tremor in the dominant hand. Mean reduction in tremor score of the treated hand was 89·4% at 1 month and 81·3% at 3 months. This reduction was accompanied by functional benefits and improvements in writing and motor tasks. One patient had postoperative paraesthesias which persisted at 3 months. Another patient developed a deep vein thrombosis, potentially related to the length of the procedure.

Interpretation MR-guided focused ultrasound might be a safe and effective approach to generation of focal intracranial lesions for the management of disabling, medication-resistant essential tremor. If larger trials validate the safety and ascertain the efficacy and durability of this new approach, it might change the way that patients with essential tremor and potentially other disorders are treated.

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brain stimulation there is also the possibility of adverse effects induced by electrical stimulation, long-term hardware breakage or malfunction, and inevitable battery depletion with time.\textsuperscript{11} To mitigate these risks and drawbacks, another procedure—radiosurgical thalamotomy—has emerged as a potential non-invasive alternative. Gamma knife radiosurgery (Elekta, Stockholm, Sweden) involves focusing multiple beams of radiation from cobalt sources on to brain targets without opening the skull.\textsuperscript{12–15} Although this technique has certain advantages over open procedures, the biological and clinical responses to radiosurgery are variable, and there is no immediate way to verify that the correct target has been reached or that a sufficient volume of thalamic tremor cells has been treated. Perhaps the most important limitation of radiosurgery is the substantial delay in the appearance of clinical effects by weeks to months, which means that the lesion location and size cannot be readily adjusted to the patient’s response during the procedure. Because the size of radiosurgical lesions can be unpredictable, the lack of immediate feedback during treatment is potentially problematic, with smaller than expected or misplaced lesions being ineffective and lesions that are larger than anticipated having the potential to spill over on to eloquent areas, producing adverse effects.\textsuperscript{16} Improved therapies for essential tremor are clearly desirable.

Focused ultrasound has been used to treat several pathologies including uterine fibroids and bony metastases.\textsuperscript{16,17} Additionally, its use in the brain has been initiated for treatment of brain tumours and for creating lesions in the intralaminar thalamic nuclei to treat pain.\textsuperscript{18–20} Treatment for tremor has also been suggested.\textsuperscript{21} Here we describe a novel thalamotomy procedure for the treatment of disabling tremor using MR-guided focused ultrasound.

Methods

Patients

Our study was done in Toronto, Canada, between May, 2012, and January, 2013. Four patients with essential tremor were included in the study. Patient inclusion and exclusion criteria are shown in panel 1. All patients were referred to the study by neurologists specialising in movement disorders, and were on stable doses of antitremor medications for at least a month before the intervention, with no medication changes occurring in the follow-up period. The patients were refractory to medical treatment and otherwise eligible for surgical treatment including thalamotomy, gamma knife treatment, or deep brain stimulation.

Those meeting the inclusion criteria (panel 1) were enrolled in the study and underwent a screening visit, including baseline tremor assessment and neuroimaging. Ten patients were screened, and six patients were excluded owing to age, minimal tremor severity, diagnosis other than essential tremor, or previous neurosurgery. Recruitment of the four patients took roughly 6 months. Patients underwent neurological examination, tremor assessment, and structural MRI scanning at 1, 30, and 90 days after the procedure. Measured outcomes were tremor severity in the treated arm and functional impairment, as well as rates of adverse events. No patients withdrew consent once it was obtained, and all patients completed all study visits.

This study received full ethics approval from the Research Ethics Board at Sunnybrook Health Sciences Center (Toronto, ON, Canada). All patients provided signed informed consent forms before the initiation of study investigations.

Procedures

The thalamus contralateral to the most disabled hand was targeted. Tremor severity and functional impairment were assessed with the clinical rating scale for tremor (CRST) at baseline and at 1 month and 3 months after surgery.\textsuperscript{22} Adverse effects were sought and ascertained by open-ended and directed questions and by neurological examination.

A stereotactic frame (CRW, Integra, Plainsboro, NJ, USA) was fixed to the skull using local anaesthesia. Patients were awake, lying supine on the MRI table with their heads coupled to the focused ultrasound device throughout the procedure. T2-weighted spin echo images of the brain were obtained using a 3-Tesla MRI scanner (General Electric, Milwaukee, WI, USA) and the presumptive site of the Vim nucleus (15 mm from midline or 11 mm from the lateral wall of the third ventricle, 7 mm anterior to the posterior commissure and at the depth of the intercommissural line) was identified. Lesions were made using a focused ultrasound transducer (650 kHz system, ExAblate Neuro, InSightec, Haifa, Israel) with simultaneous MRI. Lesions were made for 10–25 s and at 300–1250 W of acoustic power.

Patients underwent serial thalamic lesioning by heating a 2 mm diameter volume of tissue with short low-energy sonications, producing focal heating to 44°C and progressing incrementally to produce increasingly larger concentric lesions. This technique uses 1024 transducers, which transmit ultrasound energy through the skull and are focused on to a precise focal spot in the thalamus, resulting in a highly localised region of heating, thereby creating an ablative lesion. During sonications, changes in tissue temperature at target were closely tracked using proton resonance frequency-based MRI thermometry (slice thickness 3 mm, in-plane resolution 1 mm, temporal resolution 3·5 s) and measured as the average of 3×3 pixels around the target (27 mm$^3$ volume). Lesion size, location, and clinical effects were continuously monitored, with particular attention to changes in tremor in the treated arm and questioning patients during sonications for any reported adverse effects. Lesions were progressively enlarged by increasing the temperature or duration of...
sonications until either tremor suppression was achieved or adverse effects (eg, paraesthesias) were encountered. Small focal lesions created with sonications at lower acoustic power and expected to have transient effects also served as a safety test of the clinical consequences of making larger lesions, with the appearance of paraesthesias during sonication leading to a reappraisal and tailoring adjustment of the focal target usually by 1–2 mm in the anterior direction to avoid encroaching on adjacent sensory pathways. Patients were questioned and examined for anti-tremor and adverse effects (eg, numbness, pain) after each sonication. Patients had 12–29 sonications in 0, 1, or 2°C increments each over 10–25 s. At the conclusion of treatment, the frame was removed, and patients were kept in hospital overnight for monitoring. All patients were discharged the next morning. They underwent serial MRI and clinical evaluations of their tremor directly after the procedure and at 1 and 3 months after the intervention.

Role of the funding source
The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
There was a substantial improvement in tremor in all four patients during the sonifications. The benefits on tremor first appeared with a threshold thalamic tissue temperature at the Vim target reaching 50°C. These improvements were obvious, immediate, and progressive with each additional sonication that raised the tissue temperature at target above threshold. With careful monitoring, serial sonications were applied until there was complete or near complete cessation of tremor in the target arm. This required a total number of sonications ranging from 12 to 29, each lasting from 10 to 25 s (table 1). Tremor arrest was achieved in each patient, verified by having the patient hold out their arms, do a finger to nose pointing task, and draw spirals with a pen on paper (figure 1) while still in the MR-guided focused ultrasound apparatus. Patients were assessed immediately after the procedure once out of the scanner. Video footage of patient 2 undergoing tremor was obvious, immediate, and progressive with each sonication. Patients had 12–29 sonications in 0, 1, or 2°C increments each over 10–25 s. At the conclusion of treatment, the frame was removed, and patients were kept in hospital overnight for monitoring. All patients were discharged the next morning. They underwent serial MRI and clinical evaluations of their tremor directly after the procedure and at 1 and 3 months after the intervention.

Panel 1: Patient inclusion and exclusion criteria

Inclusion criteria
- Aged between 18 and 80 years
- Able and willing to give consent and able to attend all study visits
- A diagnosis of essential tremor as confirmed from clinical history and examination by a movement disorder neurologist; may have bilateral appendicular tremor
- Tremor refractory to adequate trials of at least two medications, one of which should be either propranolol or primidone. An adequate medication trial is defined as a therapeutic dose of each medication or the development of side-effects as the medication dose is titrated
- The Vim region of the thalamus must be apparent on MRI such that targeting can be done with either direct visualisation or by measurement from known anatomic landmarks
- Able to communicate sensations during treatment
- Postural or intention tremor severity score of 2 or more in the dominant hand or arm as measured by the clinical rating scale for tremor (CRST)22
- Stable doses of all medications for 30 days prior to study entry and for the duration of the study
- Substantial disability due to essential tremor despite medical treatment (CRST score of 2 or above in any one of the items on the disability subsection of the CRST)

Exclusion criteria
- Unstable cardiac status including:
  - Unstable angina pectoris on medication
  - Myocardial infarction within 6 months of protocol entry
  - Congestive heart failure requiring medication (other than diuretic)
  - On antiarrhythmic drugs
  - Severe hypertension (diastolic blood pressure >100 mm Hg on medication)
  - Standard contraindications for MRI such as non-MRI compatible implanted metallic devices including cardiac pacemakers, size limitations, etc
  - Known intolerance or allergies to the MRI contrast agent including advanced kidney disease
  - Cerebrovascular disease (multiple strokes or stroke in previous 6 months)
  - Not able or willing to tolerate the required prolonged stationary supine position during treatment
  - Unable to communicate with the investigator and staff
  - Presence of any other neurodegenerative disease such as Parkinson-plus syndromes suspected on neurological examination, including multiple system atrophy, progressive supranuclear palsy, dementia with Lewy bodies, or Alzheimer’s disease. The presence of some mild parkinsonian features will be accepted because essential tremor is recognised to be associated with overlapping symptoms of Parkinson’s disease. Mild Parkinson’s disease symptoms tolerated for inclusion are resting tremor, bradykinesia, and rigidity
  - Presence of significant cognitive impairment as determined by a score of 24 or less on the mini-mental state examination
  - History of seizures within the past year
  - Brain tumours
  - Psychiatric illnesses that are not well controlled. Any participants with presence of psychosis will be excluded. Patients with mood disorders including depression will be excluded if they have exhibited symptoms in previous 6 months while on medication
  - Risk factors for intraoperative or postoperative bleeding (platelet count less than 100 000 per mm3) or a documented coagulopathy
  - Pregnancy or lactation
  - Unable to provide consent for any reason; legal incapacity or limited legal capacity
  - Previous deep brain stimulation or a prior stereotactic ablation of the basal ganglia
Patients also had substantial improvements in their self-rated functional impairments after MR-guided focused ultrasound, showing a mean 51.1% reduction in perceived functional disability related to tremor in all four patients at 3 months, as measured by part C of the CRST scale. All patients were able to use their dominant hand to write their name and date, as well as drink from a cup without the aid of a straw at 3 months, neither of which were possible in any of the patients before surgery.

We carefully screened for sensory and motor changes during the procedure to obtain direct measures of the physiological effects and acquire brain mapping information elicited by the sonication. Two patients (patients 1 and 2) developed paraesthesias during sonication, presumably related to lesion spread to afferent sensory axons or the sensory relay nucleus of the thalamus. In patient 1 they resolved after the completion of each sonication but in patient 2 they persisted, and we decided not to make any further lesions. Patient 2 had paraesthesias in the tips of the thumb and index finger which persisted at the 3-month follow-up. The other patients had improvement of their tremor without neurological adverse effects.

The appearance of the MR-guided focused ultrasound lesion on MRI is shown in figure 2. The appearance of the acute lesion suggests an area of central necrosis surrounded by vasogenic oedema. With time, the perilesional oedema cleared and the lesion size diminished from a mean diameter (n=4) of 6.3 mm on the first postoperative day to 4.2 mm at 3 months. The procedures lasted 5–6 h including frame application, patient positioning, alignment of the focused ultrasound beams to target, calibration of the device, and serial sonications and post sonication imaging. One patient (patient 1) developed a lower limb deep vein thrombosis around 1 week after the procedure, which required anticoagulation treatment for 3 months. This event might have been related to the length of the procedure.

**Discussion**

MR-guided focused ultrasound provided effective tremor relief with an acceptable profile of adverse effects in four patients. On the basis of the clinical benefits we observed with this non-invasive procedure, we believe that MR-guided focused ultrasound could represent a substantial advance for the management of disabling tremor.

The size, location, and radiological features of the lesions on MRI are similar to those seen with thermal thalamotomy lesions made with radiofrequency electrodes. Such thalamotomies can produce clinical benefits lasting many years. We have no reason to believe that MR-guided focused ultrasound thalamotomies would be different, and indeed, the tremor control rates we noted at 3 months are similar to those seen in previous studies of both stereotactic thalamotomy and deep brain stimulation (panel 2). The profile of lesion-related adverse effects is also predicted to be similar to that of conventional radiofrequency thalamotomy, and includes sensory impairment, motor weakness, dysarthria, ataxia, dystonia, speech disturbance, and memory loss, which might occur if mis-targeting should occur or if the lesions are too large and spill over on to unwanted adjacent structures. Conversely, MR-guided focused ultrasound should reduce the risk of intracranial haemorrhage and infection, because there are no incisions and no electrode penetrations through the brain.

The ability to apply sonication to raise tissue temperature to produce transient physiological effects

<table>
<thead>
<tr>
<th>Sex</th>
<th>Treated hand</th>
<th>Age (years)</th>
<th>Illness duration (years)</th>
<th>Medication at surgery</th>
<th>Number of sonications</th>
<th>Maximum temperature achieved (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>M R</td>
<td>71</td>
<td>6</td>
<td>Propranolol, Primidone, Gabapentin</td>
<td>27</td>
<td>56</td>
</tr>
<tr>
<td>Patient 2</td>
<td>M L</td>
<td>77</td>
<td>25</td>
<td>Primidone, Propranolol</td>
<td>22</td>
<td>63</td>
</tr>
<tr>
<td>Patient 3</td>
<td>M R</td>
<td>77</td>
<td>20</td>
<td>Primidone</td>
<td>12</td>
<td>59</td>
</tr>
<tr>
<td>Patient 4</td>
<td>M R</td>
<td>58</td>
<td>20</td>
<td>Propranolol</td>
<td>29</td>
<td>59</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>70.8</td>
<td>17.8</td>
<td></td>
<td>22.5</td>
<td>59.3</td>
</tr>
</tbody>
</table>

Table 1: Patient demographics and clinical characteristics
without creating a permanent lesion permits mapping of the thalamus, facilitating accurate lesion placement and the avoidance of adverse events. Of note, although real-time imaging and the clinical effects of sublesional sonications facilitate targeting with MR-guided focused ultrasound, a shortcoming of the procedure is the absence of direct neurophysiological recording and stimulation mapping, which are possible with radiofrequency electrode lesion and deep brain stimulation surgery. Whether this limitation will affect its use at other potential targets, such as the subthalamic nucleus or the globus pallidus, where direct physiological measures combined with imaging have guided surgery at most centres, remains to be seen. Similarly, the long-term efficacy, use of health-care resources, possible need and feasibility of repeat surgery with recurrence, and safety of MR-guided focused ultrasound will require further study.

With regards to safety, one of our patients experienced paraesthesias persisting at 3 months which we attribute to the lesion extending to the sensory pathways lying posterior and ventral to Vim. Such adverse events are not unique to MR-guided focused ultrasound and occur with other forms of surgical therapy in tremor, including Vim deep brain stimulation, which can be associated with paraesthesias in 79.2% of patients at 3 months and 20.8% of patients at 1 year.28 Another patient developed a deep vein thrombosis, potentially related to the length of the procedure. With technological advances in imaging software allowing easier positioning and target localisation and with more experience of the treatment team, the procedure time will decrease substantially and the occurrence of adverse effects could decrease.

Characterisation of the changes in lesion volume will be important in the long term. We noted a gradual decrease in lesion size with MR-guided focused ultrasound thalamotomy over time. There are, however, reports of increases in lesion size with time in some patients undergoing gamma knife thalamotomy which can be accompanied by progressive neurological deficits.29 Although not seen in our limited study, or within a year of MR-guided focused ultrasound thalamotomy for pain,29 or after conventional thermal thalamotomy using radiofrequency, the occurrence of this potentially serious adverse event will have to be monitored.

All patients in this study had unilateral procedures directed at treating the dominant arm. As with other forms of thalamotomy, we do not advocate bilateral MR-guided focused ultrasound thalamotomy because this would be expected to produce unacceptable high incidence of adverse effects, chiefly a 20–30% risk of speech disturbances.30 Patients requiring bilateral procedures may be better served with at least one hemisphere having a reversible intervention such as deep brain stimulation, which can be adjusted or turned off should adverse effects related to bilateral treatments arise.

The detailed mechanisms of action through which the sonications produce tremor relief are not known. The simplest explanation is that improvement is related to the
Panel 2: Research in context

Systematic review

We did a PubMed search using the terms “essential tremor” in combination with each of “neurosurgery”, “thalamotomy”, “radiosurgery”, “gamma knife”, “focused ultrasound”, “stimulation”, and “deep brain stimulation”. We restricted our results to peer-reviewed reports that examined the safety and efficacy of neuromodulation for essential tremor in humans. We did not find any published reports of MR-guided focused ultrasound for the management of essential tremor. We found 14 papers examining gamma knife radiosurgery for essential tremor, consisting of case reports, prospective case series, and long-term follow-ups including one blinded evaluation study, and one multicentre study. There were 55 publications examining deep brain stimulation or other stimulation-based technologies in the context of essential tremor, of which 37 specifically examined the safety and efficacy of deep brain stimulation on tremor control. Two studies directly compared deep brain stimulation with stereotactic thalamotomy, with one additional study providing a double-blinded assessment of the efficacy of deep brain stimulation on essential tremor.

Interpretation

Our study is the first to show that MR-guided focused ultrasound might non-invasively generate safe and effective therapeutic thalamic lesions in patients with treatment-refractory essential tremor. Although stereotactic thalamotomy is an established and effective procedure for controlling tremor, it is nevertheless associated with attendant surgical risks. Deep brain stimulation, a non-destructive alternative to thalamotomy, is also effective, but it too can be associated with surgical and stimulation-induced adverse effects and device-related complications. Gamma knife radiosurgery has been examined as a non-invasive means of generating cerebral lesions in essential tremor, but its effects can be variable and somewhat unpredictable. Additionally, the effects of radiosurgery thalamotomy are delayed, requiring weeks to months to become noticeable, not allowing adjustments of lesion location or radiation dose based on clinical feedback. By contrast, the effects of MR-guided focused ultrasound are immediate, detectable while the patient is in the MRI scanner; furthermore, lesion location, size, and temperature can be monitored in real time and adjusted based on the clinical response during sonication. The application of sublesional temperatures further facilitates the surgeon’s ability to map the thalamus using patient feedback, to optimise lesion placement. Our results with MR-guided focused ultrasound show tremor control rates that might be comparable with those of other thalamotomy techniques or deep brain stimulation, but without the need for invasive surgery.

Although we have initiated MR-guided focused ultrasound in the context of medication-resistant disabling essential tremor, other forms of tremor and indeed other targets of neurological and psychiatric relevance could be considered in the future.

This pilot study has several important limitations. Our sample size is small, but the results show a large effect on tremor reduction that is remarkably robust and similar between patients. Additional studies with larger cohorts will be required to obtain a more accurate appraisal of long-term efficacy as well as the adverse effects profile of MR-guided focused ultrasound for essential tremor. Questions surrounding the window of safety for acoustic power and maximum safe tissue temperature and sonication time need to be addressed. For example, we were careful not to exceed 63°C, because this temperature could potentially be associated with cavitation and increased risk of haemorrhage. Additionally, our follow-up period was limited to 3 months. Such a time-period might be, however, long enough to show both the short-term and likely the longer-term safety of MR-guided focused ultrasound in patients with refractory essential tremor. In view of the similarity of the appearance of the lesions on MRI, we predict that the durability of benefits of MR-guided focused ultrasound thalamotomy could parallel that of conventional radiofrequency thalamotomy.

MR-guided focused ultrasound has several potential advantages over alternative techniques for the treatment of medication-resistant severe tremor. First, unlike radiofrequency thalamotomy and deep brain stimulation, it is non-invasive, done without a skin incision or opening the skull. Second, the procedure is done in an MRI environment where the ablating temperature can be selected and monitored in real time using MRI thermography and the lesion size and its location in the thalamus can be precisely visualised with MRI, enabling immediate adjustments and repositioning if necessary.

The application of sublesional temperatures to produce reversible physiological effects, presumably by rendering neural elements including thalamic neurons temporarily inactive, further allows surgeons to map the thalamus, thereby reducing the risk of adverse events secondary to misplacement of lesions. Third, unlike radiosurgery the clinical effects of MR-guided focused ultrasound thalamotomy are immediate, allowing adjustment of the lesion size and location according to the patient’s ongoing clinical response during the procedure. Additionally, MR-guided focused ultrasound thalamotomy does not require the implantation of permanent hardware, with associated patient visits for stimulator parameter adjustment and replacement of depleted batteries, as does deep brain stimulation.

MR-guided focused ultrasound is a non-invasive means of generating intracranial lesions and potentially providing an immediate benefit to patients with disabling essential tremor. The clinical effects may be robust and seem to be predictable, sustained, and associated with substantial improvements in functional impairment. Although promising, conclusions on safety and efficacy
References


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