Predicting lesion size during focused ultrasound thalamotomy: a review of 63 lesions over 3 clinical trials

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OBJECTIVE The goal of this study was to improve the predictability of lesion size during focused ultrasound (FUS) thalamotomy procedures.

METHODS Treatment profiles and T2-weighted MRI (T2 MRI) studies obtained in 63 patients who participated in 3 clinical trials of FUS thalamotomy from February 2011 to March 2015 were reviewed retrospectively. Four damage estimate models were compared with lesion sizes measured on postprocedural T2 MRI. Models were based on $54^{\circ}\text{C} \times 3$ seconds, 240 cumulative equivalent minutes at 43°C , and simple thermal threshold analysis, which recorded the maximum diameter that reached a temperature of at least 51°C and 54°C . Energy requirements per $^{\circ}\text{C}$ thermal rise above 37°C were also recorded.

RESULTS Lesion diameters from T2 MRI correlated poorly from the day of the procedure to day 1 postprocedure (mean increase 78% [SD 79%]). There was more predictability of lesion size from day 1 to day 30, with a mean reduction in lesion diameter of 11% (SD 24%). Of the 4 models tested, the most correlative model to day 1 findings on T2 MRI was a 51°C threshold. The authors observed an increase in the energy requirement for each subsequent treatment sonication, with the largest percentage increase from treatment sonication 1 to treatment sonication 2 (mean increase 20% in energy required per $^{\circ}\text{C}$ increase in temperature above 37°C).

CONCLUSIONS At the margins, 51°C temperature threshold diameters correlated best to lesion diameters measured at day 1 with T2 MRI. The lesion size from T2 MRI decreases from day 1 to day 30 in a predictable manner, much more so than from the day of the procedure to day 1 postprocedure. Energy requirements per $^{\circ}\text{C}$ rise above 37°C continuously increase with each successive sonication.

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KEY WORDS focused ultrasound; thalamotomy; thermal dose; tremor

FOCUSED ultrasound (FUS) thalamotomy was recently approved by the FDA for the treatment of essential tremor (ET), using a commercially approved MR-guided FUS system (ExAblate 4000; InSightec Ltd.), and is under investigation for other applications.⁹ However, the technology is still relatively new and the ability to reliably predict lesion size during the procedure is still evolving. Thermal lesion size is currently estimated from both a peak temperature of 54°C for 3 seconds and a 240 cumulative equivalent minutes (CEM) at 43°C model.

In this paper we reviewed the results in 63 patients who

underwent FUS thalamotomy over 3 clinical trials. Damage estimates from the 2 thermal dose models and simple temperature threshold models were compared with postprocedure MRI studies, and the evolution of the lesioning process was quantified from MRI.

Methods

Clinical Trial Data

Data from 3 previous FUS thalamotomy trials were reviewed retrospectively, with institutional review board

ABBREVIATIONS AC-PC = anterior commissure–posterior commissure; AP = anteroposterior; CEM = cumulative equivalent minutes; ET = essential tremor; FUS = focused ultrasound; RCT = randomized controlled trial; SDR = skull density ratio.

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FIG. 1. **A:** An MR thermometry study obtained during a sonication. **B:** Example of an image obtained using temperature thresholding. Area in red represents the area that reached a minimum defined temperature. Measurements of the diameter of this area were used in the 51°C and 54°C temperature threshold models. **C:** Example of image obtained using the 54°C × 3 seconds model (purple), and the 240 CEM at 43°C model (slate gray).

approval. The first trial was an open-label, pilot study conducted in 15 patients with ET in 2011.³ The second ET trial was a randomized sham-controlled trial (RCT), with 14 patients treated in the blinded phase and another 9 treated during the open-label extension period.⁵ The last was an RCT that was a pilot study of 25 patients treated for tremor-dominant Parkinson disease.¹ Although the RCTs included multiple sites, only the patients treated at the University of Virginia were included in this analysis. Targeting and techniques for creating an FUS thalamotomy were consistent among all 3 trials, for a total of 63 patients treated with FUS thalamotomy over 4 years. The clinical trials were registered with ClinicalTrials.gov database (<http://clinicaltrials.gov>), and their registration nos. are NCT01304758, NCT01827904, and NCT01772693.

The FUS Thalamotomy Procedure

All patients underwent unilateral FUS thalamic lesioning of the ventralis intermedius nucleus by using the ExAblate 4000 midfrequency head transducer (InSightec Ltd.) operating at 710 kHz. Details of the procedure have been described previously.^{2,3,5–7} This system calculates the temperature change from a baseline of 37°C (the assumed temperature of the brain parenchyma) during the procedure with voxel-based MR thermometry in predesignated 2D planes, which is used to adjust subsequent sonication parameters and location to obtain an adequate lesion size at a prespecified target (Fig. 1A).

Sonication Temperatures and Thermal Dose Estimates

The system has a playback mode, which was used to review the treatments. Care was taken to ensure that background temperature windows were drawn consistently in all patients, and were redrawn as necessary. Peak voxel temperature, average peak voxel temperature, target location relative to the posterior commissure (PC), sonication power, and sonication time were recorded for each sonication, which reached a background corrected average temperature of at least 50°C. At the peak temperature time point (typically the end of the sonication duration), the temperature threshold of the viewer was adjusted to a desired temperature (51°C as an example) for assessment of how much area achieved, at a minimum, the desired temperature. These 2D threshold temperature images were

used to measure the maximum diameter of tissue that exceeded the set temperature threshold in the anteroposterior (AP), lateral, and superoinferior directions (Fig. 1B); this dimension is recorded as the temperature threshold diameter. The plane of the thermal map was chosen at the time of treatment. For axial temperature maps, both the AP and lateral dimensions were recorded. To facilitate comparisons to axial MRI, when coronal or sagittal planes were used, coronal lateral dimensions and sagittal AP dimensions were included in the final analysis, and superoinferior dimensions were recorded but not used. Temperature threshold diameters were recorded using a 54°C and a 51°C threshold set point for all patients. Thresholds of 54°C and 51°C were chosen to closely match the previous 54°C × 3 seconds model, and were based on early observations of correlation of lesion size with 51°C. All measurements were superimposed on top of each other to achieve a maximum diameter of tissue that reached the threshold temperature, accounting for changes made to the target location during subsequent sonications. As an example, if sonication 7 had a temperature threshold diameter of 4 mm that reached at least 51°C and sonication 8, which was at the same target, had 5 mm, then the final temperature threshold diameter for 51°C would be recorded as 5 mm. If sonication 8 was translated 1 mm, then the final temperature threshold diameter for 51°C would be recorded as 5.5 mm [(4 mm ÷ 2) + 1 mm translation + (5 mm ÷ 2)].

Tissue damage estimates performed using 2 algorithms were also calculated by the system. The first algorithm records the voxels that reached 54°C for at least 3 seconds, and the second algorithm uses the concept of thermal dose and calculates the voxels that reach 240 CEM at 43°C (Fig. 1C). The damage estimate from each algorithm was recorded at the completion of each treatment session by measuring the maximum AP and lateral diameter in the axial plane. In the event that the thermal plane during the final sonication was in the coronal or sagittal plane, then only the lateral (coronal) or AP (sagittal) dimensions were used in the final analysis.

In summary, 4 thermal damage estimate predictive models were recorded retrospectively from the temperature measures in the workstation, as follows. 1) The 51°C threshold: amount of tissue heated beyond 51°C during a sonication; 2) the 54°C threshold: amount of tissue heated beyond 54°C during a sonication; 3) 54°C × 3 seconds:

FIG. 2. A: The T2 MRI evolution over time. Diameter measurements in the AC-PC plane were used when correlating to thermal models. Lesion size evolves over time, with mean zone 2 areas of 9.6 mm² (day 0), 21.6 mm² (day 1), 20.4 mm² (day 30), and 10.7 mm² (1 year). **B:** Box-and-whisker plot showing the mean percentage change in zone 2 lesion diameter from the day of the procedure (day 0) to day 1, and from day 1 to day 30. Asterisks represent outliers.

amount of tissue heated to 54°C for a minimum of 3 seconds; and 4) 240 CEM at 43°C: amount of tissue heated to a thermal dose of 240 CEM at 43°C.

Lesion Size Measurement From MRI

Postprocedure T2-weighted MRI (T2 MRI) studies were reviewed and measured in the axial plane at the level of the anterior commissure–posterior commissure (AC-PC) line (Fig. 2A). Lesions were assessed based on the 3 concentric zones that occur on MRI during the thermal ablation process.^{4,10} Zone 1 represents the hypointense central necrotic core, zone 2 is the surrounding T2 hyperintense cytotoxic edema region, and zone 3 is the less hyperintense T2 region corresponding to perilesional edema that resolves rapidly over time. The AC-PC length, lesion center relative to the PC, and the lateral and AP diameter of regions 1 and 2 were recorded in the AC-PC plane. The MR images were obtained on the day of the procedure, day 1, day 30, and day 90 during the open-label ET trial. For the ET RCT, MR images were obtained on the day of the procedure and at 1-year follow-up. For the ET RCT open-label extension, they were obtained on day 1. For the tremor-dominant Parkinson disease RCT, MR images were obtained on the day of the procedure, day 1, day 30, and at 1 year.

The lesion diameters observed on MRI in the AC-PC plane were compared with the temperature threshold contour maps and the workstation-simulated damage estimates with linear regression. Change in lesion size over time was calculated from MRI results by using paired t-tests.

The amount of energy required per °C rise in temperature (Energy/°C) was calculated for each sonication, which reached a maximum background corrected average temperature of at least 50°C with the following formula: $\text{Energy}/^{\circ}\text{C} = (\text{Sonication power} * \text{Sonication time}) / (\text{Max Average Temp} - 37^{\circ}\text{C})$. The percentage increase

in Energy/°C from the preceding sonication was calculated as follows: $\text{Percentage increase in Energy}/^{\circ}\text{C}_{(n)} = [\text{Energy}/^{\circ}\text{C}_{(n)} - \text{Energy}/^{\circ}\text{C}_{(n-1)}] \div [\text{Energy}/^{\circ}\text{C}_{(n-1)}]$.

Statistical Analysis

Statistical analysis was performed with IBM SPSS Statistics (version 23; IBM Corp.). Statistical significance was set at $p < 0.05$.

Results

For all lesions, the 51°C threshold model predicted mean lesion diameters in the AC-PC plane of 5.1 mm (SD 1.5 mm, range 1.5–9.5 mm); the 54°C threshold model predicted mean lesion diameters of 3.1 mm (SD 3.1 mm, range 0.0–6.3 mm); the 54°C × 3 seconds model predicted mean lesion diameters of 3.2 mm (SD 1.5 mm, range 0.0–7.2 mm); and the 240 CEM at 43°C model predicted mean lesion diameters of 6.4 mm (SD 2.0 mm, range 1.5–13.3 mm).

Figure 2A demonstrates an example of the MRI lesion evolution over time. In MRI region 2, the mean lesion diameters in the AC-PC plane on the day of the procedure were 3.5 mm (SD 1.1 mm, range 1.1–6.8 mm), on day 1 they were 5.5 mm (SD 1.6 mm, range 2.0–10.2 mm), and on day 30 they were 4.7 mm (SD 1.3 mm, range 2.3–8.5 mm). Figure 2B shows the mean percentage changes in lesion size from the day of the procedure to day 1, and from day 1 to day 30. On the day of the procedure the central necrotic region (region 1), the surrounding cytotoxic edema (region 2), and the perilesional edema (region 3) are readily apparent. By day 1, region 2 increases by a mean of 78% (SD 79%) and the perilesional edema decreases. Region 2 decreases from day 1 to day 30 by 11% (SD 24%) and the perilesional edema is no longer present; further reduction is noted by 1 year. The MRI results at 1 year were difficult to visualize in most cases due to cavity collapse, and are not reported.

TABLE 1. Simple linear regression analysis of day 1 T2-weighted MRI region 2 lesion diameter versus predictive model

Predictive Model	Linear Regression Analysis					p Value
	R ²	β	95% CI for β	B	95% CI for B	
51°C threshold	0.437	0.670	0.493–0.847	2.056	1.102–3.010	<0.001
54°C threshold	0.478	0.756	0.572–0.941	3.177	2.551–3.803	<0.001
54°C × 3 sec	0.217	0.437	0.243–0.630	4.132	3.442–4.821	<0.001
240 CEM at 43°C	0.150	0.285	0.127–0.444	3.697	2.637–4.757	0.001

B = bias (intercept); β = regression coefficient (slope); R² = coefficient of determination.

Table 1 lists the results of the simple linear regression analysis of the day 1 T2 MRI lesion diameter measured in the AC-PC plane versus the predicted lesion diameter based on 4 predictive models (51°C threshold, 54°C threshold, 54°C × 3 seconds, and 240 CEM at 43°C). The 54°C and 51°C threshold models had notably higher coefficients of determination (R²) and regression coefficients (slope) than the other 2 models. The 51°C threshold model had the lowest bias (intercept) of the 3 models. All models had statistically significant regression analysis with $p < 0.05$. Figure 3 is a scatterplot of the day 1 T2 MRI lesion diameter versus the predicted lesion diameter based on the 51°C threshold model. Common targeted lesion diameters range between 4 and 6 mm. When analyzing only patients with predicted lesion diameters of 4–6 mm, using the 51°C threshold model, the predicted lesion size was 4.9 mm (SD 0.56 mm), and the resulting day 1 lesion diameter was 5.6 mm (SD 1.2 mm). That is, if a target of 4–6 mm was planned based on thermal mapping using the 51°C threshold model, one would expect 95% of actual lesions to fall within 5.6 mm ± 2.4 mm, and 68% to fall within 5.6 mm ± 1.2 mm.

Figure 4A demonstrates the energy required per °C temperature rise over 37°C for sonications that reached a maximum average temperature of at least 50°C—the legend indicates the patients' skull density ratio (SDR).

FIG. 3. Scatterplot showing day 1 T2 MRI lesion diameter versus predicted lesion diameter, based on the 51°C threshold model. Actual lesion diameter = 0.44 [95% CI 0.49–0.85] * Predicted lesion diameter + 2.1 [95% CI 1.1–3.0], R² = 0.437, $p < 0.001$.

Figure 4B is a plot of the mean percentage increase in energy required per °C temperature rise over 37°C for each subsequent sonication that reached a temperature of at least 50°C. The increase in absolute energy required per °C temperature rise over 37°C increased with decreasing SDR; however, the percentage increase in energy with each subsequent sonication was similar for all SDR values. The mean percentage increase in energy required per °C temperature rise over 37°C, for all SDRs, was 20% higher during sonication 2, as compared with sonication 1. The percentage increase gradually decreased with further sonications, and by sonication 5 the mean percentage increase in energy required per °C temperature rise over 37°C was 11%, as compared with sonication 4.

Discussion

It is important to be able to predict lesion size during thermal ablation procedures like FUS thalamotomy. From this correlation study of thalamic temperature measurements performed using MR thermometry and postprocedural T2-weighted MRI, we found that lesion size is easier to predict from day 1 images than from images obtained during the procedure. The +78% change in lesion diameter from the day of the procedure to day 1 had significant variability (SD 79%), giving us poor confidence in the predictability of MR images obtained on the day of the procedure; however, the change from day 1 to day 30 was relatively small and more consistent (–11%, SD 24%). This gave us confidence that we could use the day 1 T2 MR images for our correlations and expect them to correlate well to the MRIs obtained at day 30, which are believed to be mature lesions before collapse of the cavity.¹⁰ In our current workflow, imaging after the final sonication is often delayed for a few minutes to be evident on T2 MR images. If an MRI study is performed immediately following a treatment, the lesion is often difficult to visualize. It is our routine for all patients receiving FUS thalamotomy to undergo MRI at day 1 and not necessarily other time points, because we have extensively characterized the lesions with MRI in a smaller number of patients, and the postprocedural evolution of the lesion is rather consistent.¹⁰

The predictive power (or correlation) of temperature estimates for FUS thalamic ablations was determined for 4 different models. The 54°C × 3 seconds and the 240 CEM at 43°C models had low correlation to the final outcomes. The 54°C threshold model had the best R² value and slope of all models; however, a large bias was still present (3.2 mm). The 51°C threshold model had the lowest bias of all models studied (2.1 mm) and had a similar R² to that of the

FIG. 4. A: Graph showing the energy required per °C temperature rise versus number of sonications exceeding 50°C maximum average temperature. Key indicates patients' SDR. **B:** Graph showing the mean percentage increase in energy requirement from prior sonication for all SDRs.

54°C model. From the data we collected, we can conclude that at the margins, the 51°C threshold data most closely predicts the lesion size observed on day 1 T2 MRI. Previous studies in rabbits demonstrated a peak temperature threshold between 48°C and 50.8°C, which is consistent with our findings at the margins.⁸ It is worth noting that, to achieve a 51°C thermal diameter of at least 5 mm (a rea-

sonable lesion size), a peak voxel temperature of > 56°C is generally required, which is a common goal during FUS lesioning.

We observed an increase in the energy requirement for each subsequent treatment sonication. The percentage increase in the energy requirement to achieve a given temperature was largest from sonication 1 to sonication

2 (20%), and decreased with subsequent sonications. The mechanism for the increase in required energy is unclear and is under investigation.

Limitations of this study include the fact that it was in a single center, retrospective, and that all measurements were performed by a single investigator. Strengths include the large number of patients and the spread in time in which patients were treated.

Conclusions

In this retrospective review of 63 FUS thalamotomies, lesion size from T2 MRI correlated well from day 1 to day 30, and can be used to estimate lesion diameters. During the procedure, 51°C temperature threshold diameters at the margins correlated most closely to lesion diameters measured on day 1 T2 MRI. Energy requirements per °C rise above 37°C continuously increase with each successive sonication.

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Author Contributions

Conception and design: both authors. Acquisition of data: both authors. Analysis and interpretation of data: both authors. Drafting the article: Bond. Critically revising the article: both authors. Reviewed submitted version of manuscript: both authors. Approved the final version of the manuscript on behalf of both authors: Bond. Statistical analysis: Bond. Administrative/technical/material support: Elias. Study supervision: Elias.

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