

Factors Associated with Heating Efficiency in Transcranial Focused Ultrasound Therapy

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Abstract

Transcranial magnetic resonance-guided focused ultrasound (FUS) therapy is a less invasive stereotactic treatment for tremor and other movement disorders. A sufficiently high temperature in the target brain tissue is crucial during ablation procedures for good outcomes. Therefore, maximizing the heating efficiency is critical in cases where high temperature cannot be achieved because of patient-related characteristics. However, a strategy to achieve the desired therapeutic temperature with FUS has not yet been established. This study aimed to investigate the procedural factors associated with heating efficiency in FUS. We retrospectively reviewed and analyzed data from patients who underwent FUS for ventralis intermedialis (VIM) nucleus thalamotomy. In all, 30 consecutive patients were enrolled. 18 with essential tremor (ET), 11 with tremor-dominant Parkinson's disease (TDPD), and 1 with Holmes tremor. Multivariate regression analysis showed that decline in heating efficiency was associated with lower skull density ratio (SDR) and a greater subtotal rise in temperature until the previous sonication. To maximize heating efficiency, the temperature increase should be set to the least value in the target alignment and verification phases, and subsequently should be increased sufficiently in the treatment phase. This strategy may be particularly beneficial in cases where high ablation temperatures cannot be achieved because of patient-related characteristics. Importantly, a broad patient population would benefit from this strategy as it could reduce the need for high energy to achieve therapeutic temperatures, thereby decreasing the risks of adverse events.

Keywords: focused ultrasound therapy, heating efficiency, ventralis intermedialis nucleus

Introduction

Transcranial magnetic resonance (MR)-guided focused ultrasound (FUS) therapy is a less invasive treatment in stereotactic and functional neurosurgery.^{1–4} Because FUS is a thermal ablation therapy, achieving sufficiently high temperature in the target tissue is essential to create lesions, thereby providing good therapeutic outcomes.^{5–7} However, in some cases,

achieving therapeutic temperatures may be difficult, necessitating the need for potential strategies to maximize heating efficiency.

Several patient-related factors which impede sufficient heating of the targeted spot have been reported.⁸ The skull is an effective barrier to ultrasound, and skull density ratio (SDR) is one of the significant factors that determine permeability to ultrasound.⁸ SDR is calculated as the ratio between the mean values in Hounsfield units for bone marrow and cortical bone. Deep brain targets in patients with high SDR tend to attain therapeutic temperature relatively easily. In contrast, various difficulties impede the achievement of sufficiently high temperatures in patients with low SDR. For this reason,

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the US Food and Drug Administration recommends an SDR of 0.45 or less as a contraindication for FUS treatment.^{9,10)} As reported previously, 78.6% of the study patients had SDRs of ≤ 0.40 ,¹¹⁾ which makes maximization of heating efficiency a critical clinical issue. However, a strategy to maximize heating efficiency in FUS remains to be established.

Therefore, we investigated the treatment procedure-related factors associated with heating efficiency in FUS. Identification of the ideal conditions required to achieve optimal ablation temperature would benefit patients indicated for FUS therapy, especially those with low SDRs. The study results will help to achieve increased efficacy of ablation in treating such conditions.

Methods

Patients

Patients with medication-refractory essential tremor (ET), tremor-dominant Parkinson's disease (TDPD), and Holmes tremor, as diagnosed by neurologists specializing in movement disorders, were enrolled between March 2017 and August 2019. TDPD diagnosis was defined as tremor dominant with a postural instability/gait difficulty ratio of >1.15 calculated from the Unified Parkinson's Disease Rating Scale in the "on" state according to the criteria described previously.¹²⁾ Patients were enrolled when they had a clinically significant tremor, defined as a score of more than 2 on the postural or action item on the Clinical Rating Scale for Tremor in the dominant hand, and substantial disability in the performance of daily activities, defined as a score of more than 2 in any of the disability subsections of the scale. We excluded patients with unstable cardiac conditions, cerebral tumor, intracranial aneurysm or arteriovenous fistula, cognitive impairment (as defined by a score of 24 or less on the Mini-Mental State Examination), or a history of deep brain stimulation or stereotactic cerebral ablation. We set the SDR of more than 0.25 for the screening computed tomography scan which was required for enrollment. This was lower than the US Food and Drug Administration recommended cut-off value because our patients tended to have lower SDRs.⁹⁻¹¹⁾

All the patients underwent unilateral ventralis intermedius (VIM) thalamotomy through FUS.

Ethical approval for standard protocol, clinical registrations, and patient consent

The data for this study were retrospectively collected and analyzed (University hospital Medical Information Network Clinical Trials Registry number: UMIN000033940 for TDPD). The study was conducted

with permission from the relevant Ethical Review Board in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects (Provisional Translation as of March 2015). All the patients provided written informed consent.

FUS procedure

Under local anesthesia, a stereotactic frame was attached over the skull. All patients with ET and TDPD were treated with FUS using the Exablate Neuro (Insightec, Haifa, Israel) with a 1.5-T magnetic resonance imaging system (Signa HDx, GE Healthcare, Milwaukee, WI, USA). The unilateral VIM nucleus was targeted in all cases. The target was set 6 mm anterior to the posterior commissure on the anterior commissure-posterior commissure line, 1.5 mm superior to the anterior commissure-posterior commissure plane, and 12 mm lateral to the ipsilateral wall of the third ventricle. The targeted point corresponds to the lateral part of the VIM according to the stereotactic atlas described previously.¹³⁾ During treatment, the sonication energy was increased in a stepwise fashion, while ensuring that the location, size, shape, and temperature of the ablation spot were adequate. After confirming the effects on symptoms and the absence of side effects at a temperature which provides a reversible effect, we generated a permanent lesion at a higher temperature. The procedure was terminated if the symptoms showed sufficient improvement, the temperature failed to increase further with higher sonication energy, or adverse neurological events were detected. The lesion locations and the absence of radiographic complications were assessed using MR imaging on the immediate post-procedural day.

Assessment of procedure-related factors and statistical analysis

The patient- and treatment procedure-related factors that we assessed included the age, sex, skull surface area, skull volume, SDR, number of active transducer elements, subtotal energy delivered up until the previous sonication (SubE), and subtotal temperature rise until the previous sonication (SubT). SubE was defined as the sum of energy (kJ) delivered from the first to the previous sonications. SubT was defined as the sum of temperature rise ($^{\circ}\text{C}$) from the first to the previous sonications. We considered SubT, for which the temperature rise was calculated as the maximum tissue temperature minus 37.0, was more reasonable for analyses than subtotal temperature because MR thermometry shows the tissue temperature assuming that the brain tissue is at 37.0 $^{\circ}\text{C}$, and thus, the tissue temperature can be different from the actual one. Heating efficiency

was calculated by dividing the difference in maximum temperature (°C) by the difference in delivered energy (kJ) between two consecutive sonications.

All statistical analyses were performed using the R statistical software package, version 3.3.3 (R Development Core Team, Vienna, Austria). We assessed the normality of distributions of continuous variables using quantile–quantile plots and the Shapiro–Wilk test. Wilcoxon rank-sum test was used for the between-group comparison of skewed continuous variables. Linear regression analysis was performed to estimate the association between heating efficiency and other factors.

Results

Participants and treatment data

We treated a total of 30 patients (18 with ET, 11 with TDPD, and 1 with Holmes tremor), and analyzed a total of 256 sonications. Patients had a mean age (\pm standard deviation) of 70.5 ± 12.0 years (range, 33–82). In all, 18 patients (60.0%) were men, and 12 (40.0%) were women. All patients had a median SDR (interquartile range) of 0.35 (0.30–0.40), skull surface area of 356 cm^2 (343.0–367.5), skull volume of 230.8 cm^3 (218.1–265.3), and the number of active transducer elements of 956 (937.5–986) in the treatment area. The targeted VIM was located in the left hemisphere in 27 patients (90.0%). The median total number of sonications was 9 (9–10). Furthermore, the median maximum delivered energy was 111.2 kJ (70.5–175.0). The median maximum temperature in the targeted spot was 58.2°C (55.5–60.6).

Heating efficiency

The results of statistical analyses are summarized in Table 1. Univariate regression analyses showed that heating efficiency was significantly associated with SDR, skull volume, and SubT. Multiple regression analysis revealed that a decline in heating efficiency was significantly associated with lower SDR and higher SubT.

Heating efficiency decreased with increase in SubT, and occasionally, showed negative values, indicating the requirement of lower maximum temperatures than those after the previous sonication even when higher energy was delivered, as shown in Fig. 1A. A similar result was observed in the groups separated according to SDRs, as shown in Fig. 1B. Those with lower SDRs had a lower heating efficiency. Multiple regression analysis also showed significant difference in heating efficiency between high SDR (≥ 0.45) and low SDR (< 0.45) patient groups ($P < 0.001$, 95% confidence interval: 0.563–1.577), while SDR was not significantly associated with SubT ($P = 0.082$).

Discussion

According to the results of our statistical analyses, the factors associated with the heating efficiency included SDR and SubT. Our findings about the correlation between heating efficiency and SubT in all groups separated according to SDRs support the results of multivariate analysis that established SubT as an independent factor. The association between lower-SDR groups and heating efficiency in turn supports the results of multivariate analysis that identified SDR as an independent factor.

To date, several reports have focused on factors associated with achieving higher temperature in the targeted spot.^{8,14,15} White et al.¹⁴ reported that skull thickness and incident angles of beam paths were some of the key factors for ultrasound waves to pass through the skull. Hughes et al.¹⁵ reported that reduced temperature rise was associated with increased high-power sonication of the target associated with the focal volume. Moreover, another study reported that SDR and skull volume negatively correlated with maximum temperatures in the targeted spot.⁸ Consequently, SDR has become an important factor for predicting treatment efficacy. However, most previously reported factors are patient-related, and thus, difficult to change, with some exceptions. A previous study reported the potential use of bisphosphonates to increase SDRs.^{16–18}

Because approximately 80% of the patients had SDRs of ≤ 0.40 , efficient strategies were needed for achieving the highest possible temperature in the target.¹¹ Despite the documented difficulties, a study previously reported that FUS can be performed successfully for patients with ET and TDPD having low-SDR.¹¹ A later report on skull factors further suggested that patients with low SDR can be successfully treated.¹⁹ While these reports indicate that it is feasible to reach sufficiently high temperatures in the target even in patients with low SDR, a reliable procedural strategy to maximize heating efficiency is not available.

Among the factors associated with heating efficiency in the current study, SubT is a treatment-related factor, which can be controlled, whereas SDR is a patient-related factor. A higher heating efficiency was associated with a smaller SubT, suggesting that minimizing temperature increase is one of the key factors for maximizing heating efficiency in FUS. We are currently unsure of the mechanisms underlying the relationship between higher heating efficiency and a smaller SubT. However, we hypothesize that an edematous state may arise in the ablated spot after repetitive cycles of temperature rise, causing decreased heating efficiency, and hence, reduced

Table 1 Univariate and multivariate analyses of factors associated with heating efficiency

Factor	Univariate		Multivariate	
	P value	Regression coefficient	95% Confidence interval	P value
Age (year)	.302			
Sex (female)	.152			
SDR	<.001	4.781	2.450–7.152	<.001
Skull surface area (cm ²)	.866			
Skull volume (cm ³)	.031	0.001	–0.004 to 0.002	0.642
No. of active transducer elements	.186			
SubE (kJ)	.663			
SubT (°C)	<.001	–0.012	–0.016 to –0.008	<.001

SDR: skull density ratio, SubE: subtotal energy delivered up until the previous sonication, SubT: subtotal temperature rise until the previous sonication.

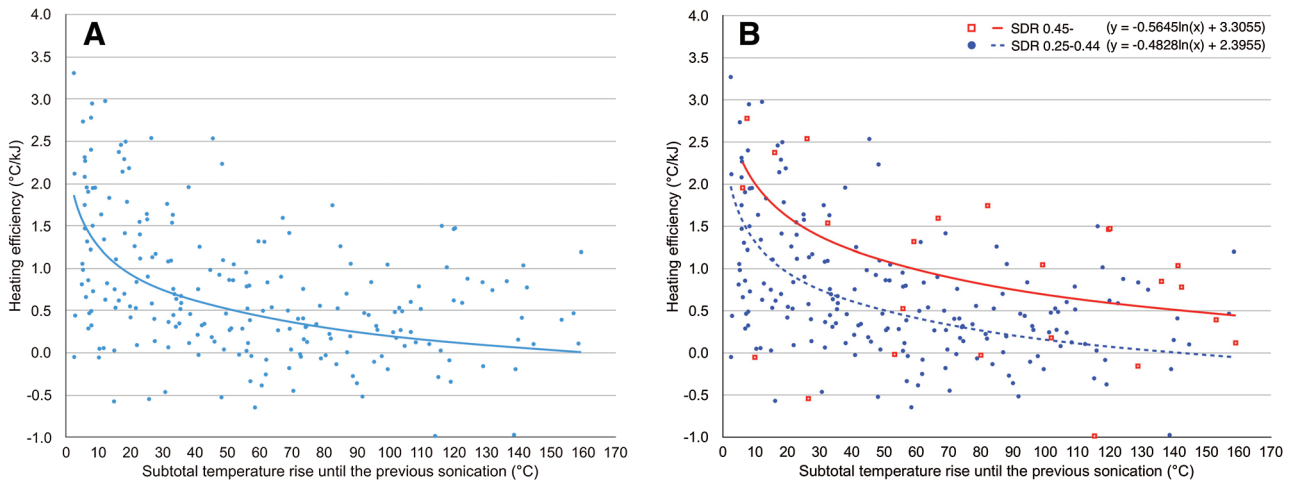


Fig. 1 Subtotal temperature rise and heating efficiency. The graphs show the association between the subtotal amount of temperature rise until the previous sonication and heating efficiency. (A) Heating efficiency declined as the subtotal amount of temperature rise until the previous sonication increased. (B) Similar findings were observed in both groups separated according to skull density ratios.

treatment efficacy. To achieve the highest possible temperature in the target, minimizing the amount of SubT in the target alignment and verification phases might be effective. While unnecessarily high temperatures in the target alignment phase lead to increase in SubT, insufficient rise in temperature prevents accurate localization of the heated spot. This calls for the need of additional sonications, which, in turn, would increase the amount of SubT. To minimize the amount of SubT, we need to control energy to achieve necessary and sufficient temperatures around 40–42°C. For the same reason, temperature rise should be bare minimum in the verification phase. Nevertheless, we need to increase the

temperature up to approximately 50°C in the target to see temporary effects and absence of adverse events. After the target alignment phase, achieving such temperature with a minimum number of sonications may preserve the heating efficiency in the treatment phase. Furthermore, setting the energy sufficiently high to achieve therapeutic temperatures immediately after the verification phase may allow the target to reach the highest possible temperature. This strategy, however, requires precise temperature control to prevent adverse events. Estimation of the appropriate energy to achieve necessary and sufficient temperatures in each phase requires experience. Additionally, further investigations should evaluate

the efficacy and safety of the above strategy. On the other hand, the equations and graphs in Fig. 1B may help estimate appropriate energy to deliver for each sonication according to the patients' SDR.

Our study has some limitations. Primarily, the number of enrolled patients is small. The retrospective study design is also a limitation, and a randomized controlled trial is warranted in future for further investigation of the factors associated with heating efficiency in FUS.

Conclusions

Our study shows that heating efficiency in FUS declines as the SubT in the targeted spot becomes larger. The findings thus suggest that minimizing the temperature rise in the target alignment and verification phases and increasing energy in the treatment phase to maximize heating efficiency may be the best strategy to achieve the highest possible temperature in the target. Even in cases where high temperatures can be achieved readily, this strategy may prove beneficial for the broader community of patients. Thus, by allowing the target to reach therapeutic temperatures through the delivery of lower energy, the risks of adverse events, such as cavitation, skull heating, skin burn, and headache, may also be mitigated.^{20,21)}

Conflicts of Interest Disclosure

All authors have no conflict of interest. All JNS member authors have registered online Self-reported COI Disclosure Statement Forms through the website.

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