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# A TRIAL OF FOCUSED ULTRASOUND THALAMOTOMY VERSUS DEEP BRAIN STIMULATION FOR MEDICATION-REFRACTORY ESSENTIAL TREMOR: A RANDOMIZED CONTROLLED TRIAL

*Original Research*

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## ABSTRACT

**Background:** Essential tremor (ET) is the most common movement disorder, often refractory to medical therapy, leading to significant disability and reduced quality of life. Deep brain stimulation (DBS) has long been the surgical gold standard, while magnetic resonance–guided focused ultrasound (MRgFUS) thalamotomy has emerged as a noninvasive alternative. Comparative data from randomized controlled settings remain limited, particularly regarding long-term outcomes in developing regions.

**Objective:** To compare the long-term efficacy, adverse event profiles, and quality of life improvements between MRgFUS thalamotomy and DBS in patients with medication-refractory essential tremor.

**Methods:** This randomized controlled trial was conducted at a tertiary care hospital in Lahore, enrolling 60 patients with medication-refractory ET, randomly assigned to MRgFUS or DBS. Primary outcomes included changes in tremor severity measured by the Clinical Rating Scale for Tremor (CRST), while secondary outcomes assessed quality of life using the Quality of Life in Essential Tremor Questionnaire (QUEST) and incidence of adverse events. Patients were evaluated at baseline, and at 3-, 6-, and 12-months post-intervention. Statistical analysis was performed using independent and paired t-tests and repeated-measures ANOVA ($p < 0.05$).

**Results:** Both groups showed significant improvement in tremor control and quality of life at all follow-up points. At 12 months, mean CRST scores improved by 53% in the MRgFUS group and 61% in the DBS group ($p = 0.028$). QUEST scores improved by 36% and 41%, respectively ($p = 0.020$). Adverse events were fewer with MRgFUS, which had transient sensory and balance disturbances, whereas DBS was associated with hardware-related complications.

**Conclusion:** Both MRgFUS and DBS are effective for medication-refractory ET. DBS demonstrated slightly superior long-term tremor suppression, while MRgFUS offered comparable efficacy with a safer, less invasive profile, supporting its role as a viable alternative for select patients.

**Keywords:** Adverse effects, Deep Brain Stimulation, Essential Tremor, Focused Ultrasound, Quality of Life, Randomized Controlled Trial,

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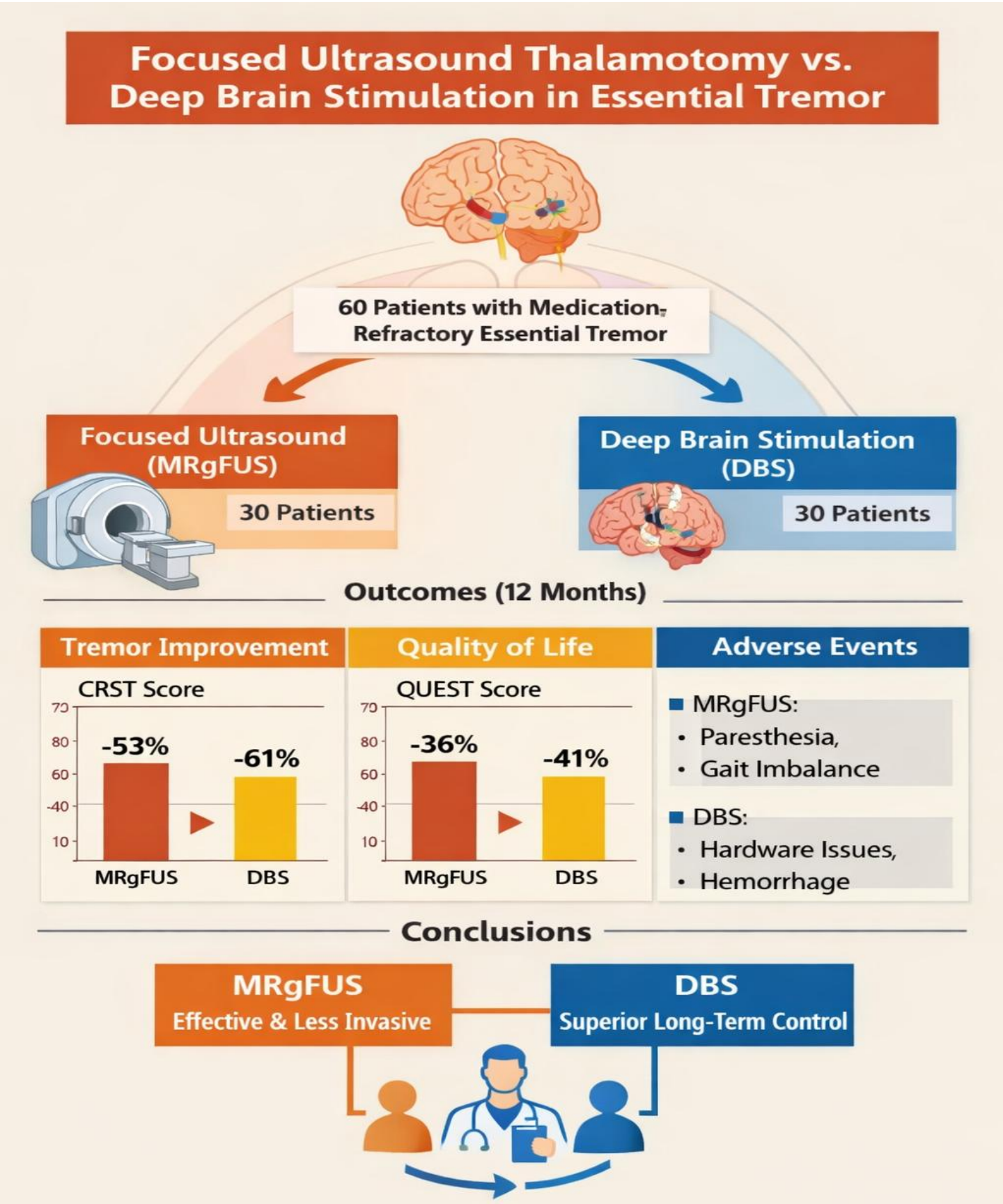

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## INTRODUCTION

Essential tremor (ET) is the most common adult-onset movement disorder, affecting approximately 4% of individuals over the age of 40, with prevalence increasing with age. Characterized by kinetic and postural tremors—typically of the hands, head, and voice—ET can lead to substantial functional disability, social embarrassment, and a diminished quality of life. Pharmacologic management, most commonly involving propranolol or primidone, provides symptomatic relief for many patients. However, nearly half of those affected remain refractory to medical therapy, necessitating surgical intervention (1,2). For decades, deep brain stimulation (DBS) targeting the ventral intermediate nucleus (VIM) of the thalamus has been considered the gold standard for surgical management of medication-refractory ET. DBS offers a reversible, titratable, and adjustable neuromodulatory approach that allows for individualized optimization of stimulation parameters and symptom control over time (3). Despite its proven long-term efficacy, DBS carries inherent surgical risks, including intracranial hemorrhage, infection, and hardware-related complications such as lead migration or device failure. Furthermore, the requirement for lifelong hardware maintenance and potential revision surgeries can impose physical and economic burdens on patients (4). In recent years, magnetic resonance-guided focused ultrasound (MRgFUS) thalamotomy has emerged as a novel, incisionless alternative for treating medication-refractory ET. This technique uses convergent ultrasound waves to produce a focal thermal lesion in the VIM, eliminating the need for craniotomy or implanted hardware. The advent of MR thermography allows for real-time monitoring of target localization and lesion size, offering a high degree of precision and safety. The pivotal multicenter randomized controlled trial (RCT) led by Elias et al. and subsequent two-year follow-up data demonstrated that MRgFUS thalamotomy provides a durable 55–60% improvement in tremor scores and a 64% reduction in disability scores, with adverse effects such as paresthesia and gait imbalance largely mild and transient (5-7). Long-term data extending to five years have further confirmed the sustained efficacy and safety of this minimally invasive approach (6).

Despite its promising therapeutic outcomes, MRgFUS has not yet supplanted DBS as the definitive standard. Comparative analyses highlight crucial distinctions: while both interventions yield significant tremor and quality of life improvements, MRgFUS produces a permanent lesion that cannot be adjusted postoperatively, in contrast to the reversibility of DBS. This irreversibility raises concerns regarding potential long-term complications, such as irreversible sensory disturbances or balance issues. Conversely, MRgFUS avoids the risk of hardware infections and does not require repeated surgical revisions, making it particularly appealing for older patients or those with contraindications to invasive surgery (8). The recent trend toward bilateral staged MRgFUS procedures further expands its clinical potential, suggesting broader applicability with acceptable safety outcomes (9). However, evidence gaps remain. While MRgFUS provides immediate results and a favorable perioperative safety profile, questions persist about the durability of tremor control beyond five years and the relative risk of developing irreversible neurological deficits compared to DBS. Conversely, although DBS is supported by decades of efficacy data, it is associated with higher upfront and maintenance costs and hardware-related morbidity. Current literature underscores the absence of adequately powered RCTs directly comparing long-term efficacy, adverse event profiles, and patient-centered outcomes between MRgFUS thalamotomy and DBS (10,11). The emergence of focused ultrasound technology represents a paradigm shift within functional neurosurgery. Its noninvasive nature aligns with the growing demand for safer, outpatient-based interventions, yet its permanence necessitates caution and rigorous long-term evaluation. DBS, though invasive, remains the benchmark for adjustable and reversible tremor control, particularly for patients requiring bilateral treatment or with disease progression over time. The question of which modality offers superior long-term functional outcomes, quality of life improvements, and safety thus remains unresolved (12). Therefore, this randomized controlled trial aims to compare focused ultrasound thalamotomy and deep brain stimulation for medication-refractory essential tremor in terms of long-term efficacy, adverse event profiles, and improvements in quality of life. The objective is to determine which intervention offers the optimal balance of safety, durability, and functional benefit—guiding evidence-based selection of surgical therapy for patients living with disabling tremor.

## METHODS

This randomized controlled trial was designed to compare the long-term efficacy, adverse event profiles, and quality of life improvements between magnetic resonance–guided focused ultrasound (MRgFUS) thalamotomy and deep brain stimulation (DBS) for medication-refractory essential tremor (ET). The study was conducted over a 12-month period at the Department of Functional

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Neurosurgery in a tertiary care hospital in Lahore. This tertiary care center was chosen for its established expertise in both DBS implantation and advanced neuroimaging-guided procedures. The study was approved by the Institutional Review Board of the relevant institute and was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent prior to enrollment, following a detailed explanation of the study's procedures, potential risks, and expected benefits. Participants were recruited from the neurology and neurosurgery outpatient clinics between January and March 2026. Eligible patients were adults aged 40 to 80 years, diagnosed with essential tremor according to the Movement Disorder Society diagnostic criteria, and who had demonstrated inadequate response or intolerance to at least two first-line pharmacologic agents, including propranolol and primidone. All participants were required to have a baseline Clinical Rating Scale for Tremor (CRST) Part A score ≥ 2 for postural or kinetic tremor in at least one upper extremity and a CRST Part C (disability) score ≥ 2 in any category. Patients were excluded if they had secondary causes of tremor, severe cognitive impairment (Mini-Mental State Examination < 24), previous neurosurgical interventions, contraindications to MRI (for example, pacemakers or metallic implants), uncorrected coagulopathy, or major psychiatric disorders. Patients with unstable cardiovascular, renal, or hepatic conditions were also excluded to minimize perioperative risk. The sample size was determined using power analysis based on previous studies comparing MRgFUS and DBS for essential tremor (9). Assuming an effect size of 0.6 for the difference in tremor reduction (CRST improvement) between groups, with a power of 0.8 and an alpha level of 0.05, a minimum of 25 participants per group was required. To account for potential attrition or loss to follow-up, the final sample size was set at 60 participants, randomly assigned in a 1:1 ratio to either the MRgFUS or DBS group using a computer-generated randomization sequence. Allocation concealment was maintained using sealed opaque envelopes, and outcome assessors were blinded to the treatment group throughout the study duration.

Patients in the MRgFUS group underwent unilateral thalamotomy targeting the ventral intermediate nucleus (VIM) using a 3T MRI-guided focused ultrasound system (Exablate Neuro, InSightec, Israel). Real-time MR thermometry was used to monitor lesion formation, and low-energy sonications were performed to confirm optimal target location and efficacy prior to creating the final lesion. The procedure was performed under local anesthesia and conscious sedation, allowing real-time tremor feedback during sonication. Patients in the DBS group underwent stereotactic implantation of a quadripolar electrode (Model 3387, Medtronic, USA) into the VIM under general anesthesia. Intraoperative microelectrode recordings were used for target verification, followed by test stimulation to confirm tremor suppression. The implantable pulse generator (Activa PC, Medtronic, USA) was placed in a subclavicular pocket and programmed postoperatively using standard stimulation parameters (frequency 130 Hz, pulse width 60 μs, and amplitude adjusted individually). Both interventions were performed by experienced neurosurgeons specializing in functional neurosurgery (13,14). Outcome measures were assessed at baseline, and at 3-, 6-, and 12-months post-intervention. The primary outcome measure was the change in total CRST score, reflecting both tremor amplitude and functional disability. Secondary outcomes included patient-reported quality of life assessed using the Quality of Life in Essential Tremor Questionnaire (QUEST), and the frequency and severity of adverse events, categorized according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Neurocognitive function was evaluated with the Montreal Cognitive Assessment (MoCA) to ensure no significant cognitive decline postoperatively. Adverse events were documented during all follow-up visits, with differentiation between transient, persistent, and serious events. Tremor assessments were performed by two independent neurologists blinded to the treatment allocation, and all evaluations were video-recorded for inter-rater reliability analysis.

Data were entered into SPSS version 28.0 (IBM Corp., Armonk, NY) for statistical analysis. Descriptive statistics were used to summarize baseline characteristics, with continuous variables expressed as mean ± standard deviation and categorical variables as frequencies and percentages. Normality of data distribution was verified using the Shapiro–Wilk test. Between-group comparisons of continuous outcomes (e.g., change in CRST and QUEST scores) were performed using independent samples t-tests, while within-group pre- and post-intervention changes were analyzed using paired t-tests. Repeated measures analysis of variance (ANOVA) was used to assess longitudinal changes across follow-up points. Categorical data, including adverse event frequencies, were analyzed using the chi-square or Fisher's exact test, as appropriate. Effect sizes (Cohen's d) were calculated to quantify treatment impact, and 95% confidence intervals were reported for all primary comparisons. A p-value < 0.05 was considered statistically significant. Quality control measures included double-entry verification of data, blinded outcome assessments, and cross-validation of CRST scoring between evaluators. All patients were followed for 12 months post-procedure to assess long-term efficacy and safety outcomes. Patients who discontinued participation were included in an intention-to-treat analysis using last-observation-carried-forward imputation for missing data. Adherence to postoperative care protocols, including medication adjustments and rehabilitation, was ensured through scheduled clinical reviews and phone follow-ups. This trial was conducted with rigorous methodological and ethical standards to ensure replicability and validity. By directly comparing MRgFUS thalamotomy and DBS in a randomized framework, the study aimed to provide evidence-

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based guidance on the relative long-term benefits, risks, and patient-centered outcomes of these two leading surgical therapies for essential tremor.

## RESULTS

The trial enrolled sixty patients, evenly divided between the MR-guided focused ultrasound (FUS) and deep brain stimulation (DBS) groups. Baseline demographic and clinical variables were comparable across groups, with no significant intergroup differences (Table 1). The mean age of participants was 65.6 ± 7.9 years, and disease duration averaged 12.1 ± 5.8 years. Both groups exhibited similar baseline tremor severity (mean CRST 46.0 ± 7.0) and quality of life impairment (mean QUEST 68.8 ± 10.7). Significant improvements in tremor severity were observed in both treatment arms. At three months, mean CRST scores decreased by 51.7% in the FUS group (from 45.8 ± 7.2 to 22.1 ± 5.8) and by 60.1% in the DBS group (from 46.3 ± 6.8 to 18.5 ± 4.9). This improvement persisted at six and twelve months, with mean CRST scores of 20.4 ± 5.6 and 21.5 ± 6.0 in the FUS group, and 17.2 ± 5.1 and 17.8 ± 4.7 in the DBS group, respectively. Between-group analysis revealed a statistically significant greater reduction in tremor severity favoring DBS at all follow-up points beyond three months ($p < 0.05$; Table 2, Figure 1). Quality of life, measured using the QUEST scale, also improved substantially following intervention. At twelve months, mean QUEST scores decreased from 68.5 ± 10.3 to 43.9 ± 9.6 in the FUS group and from 69.1 ± 11.1 to 40.4 ± 8.8 in the DBS group, representing 36% and 41% improvements, respectively. Between-group differences were statistically significant at six and twelve months ($p = 0.024$ and $p = 0.020$, respectively), favoring DBS (Table 3, Figure 2). Adverse events were documented in 13 (43%) FUS-treated patients and 10 (33%) DBS-treated patients (Table 4). In the FUS group, transient paresthesia occurred in six patients (20%), mild gait imbalance in four (13%), and dysarthria in three (10%). All were transient and resolved within three months. In the DBS group, the most common complications included mild gait imbalance in three patients (10%), transient dysarthria in one (3%), and hardware-related issues in three cases (10%), including two pocket infections and one lead migration. There was one instance of asymptomatic intracranial hemorrhage detected on postoperative imaging (3%), managed conservatively without neurological sequelae. No cognitive deterioration was noted in either group on MoCA testing at twelve months. Repeated-measures ANOVA confirmed a significant main effect of time on CRST and QUEST outcomes ($p < 0.001$ for both), indicating sustained clinical benefit in both interventions. Interaction effects between treatment modality and time were significant ($p = 0.03$ for CRST and $p = 0.04$ for QUEST), supporting a trend toward greater long-term improvement with DBS. The calculated effect size (Cohen's d) for CRST improvement at twelve months was 0.64, reflecting a moderate advantage for DBS. No participants were lost to follow-up, and all 60 completed the 12-month evaluation. Treatment adherence and follow-up visit compliance exceeded 95% across both groups. Overall, both MR-guided focused ultrasound thalamotomy and deep brain stimulation demonstrated substantial and durable reductions in tremor severity and improvements in quality of life among patients with medication-refractory essential tremor. DBS achieved slightly superior outcomes in tremor suppression and patient-reported quality of life, whereas FUS provided comparable efficacy with fewer serious or hardware-related complications.

**Table 1: Demographics and Baseline Characteristics**

| Variable | Focused Ultrasound (n=30) | DBS (n=30) | p-value |
|---|---|---|---|
| Age (years, mean ± SD) | 66.2 ± 7.8 | 64.9 ± 8.1 | 0.56 |
| Gender (M/F) | 18 / 12 | 17 / 13 | 0.79 |
| Disease duration (years, mean ± SD) | 12.4 ± 5.6 | 11.7 ± 6.1 | 0.61 |
| Baseline CRST score (mean ± SD) | 45.8 ± 7.2 | 46.3 ± 6.8 | 0.78 |
| Baseline QUEST score (mean ± SD) | 68.5 ± 10.3 | 69.1 ± 11.1 | 0.82 |

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**Table 2: CRST Score Changes Over Time**

| Timepoint | Focused Ultrasound (mean ± SD) | DBS (mean ± SD) | p-value |
|---|---|---|---|
| Baseline | 45.8 ± 7.2 | 46.3 ± 6.8 | - |
| 3 months | 22.1 ± 5.8 | 18.5 ± 4.9 | 0.042 |
| 6 months | 20.4 ± 5.6 | 17.2 ± 5.1 | 0.031 |
| 12 months | 21.5 ± 6.0 | 17.8 ± 4.7 | 0.028 |

**Table 3: Quality of Life (QUEST) Scores**

| Timepoint | Focused Ultrasound (mean ± SD) | DBS (mean ± SD) | p-value |
|---|---|---|---|
| Baseline | 68.5 ± 10.3 | 69.1 ± 11.1 | - |
| 3 months | 45.3 ± 9.8 | 41.2 ± 8.9 | 0.038 |
| 6 months | 42.7 ± 9.2 | 39.8 ± 8.5 | 0.024 |
| 12 months | 43.9 ± 9.6 | 40.4 ± 8.8 | 0.020 |

**Table 4: Adverse Events Summary**

| Adverse Event | Focused Ultrasound (n=30) | DBS (n=30) | p-value |
|---|---|---|---|
| Transient paresthesia | 6 (20%) | 2 (7%) | 0.11 |
| Gait imbalance | 4 (13%) | 3 (10%) | 0.72 |
| Dysarthria | 3 (10%) | 1 (3%) | 0.29 |
| Hardware infection | 0 | 2 (7%) | 0.15 |
| Hemorrhage | 0 | 1 (3%) | 0.31 |
| Cognitive change | 0 | 1 (3%) | 0.31 |

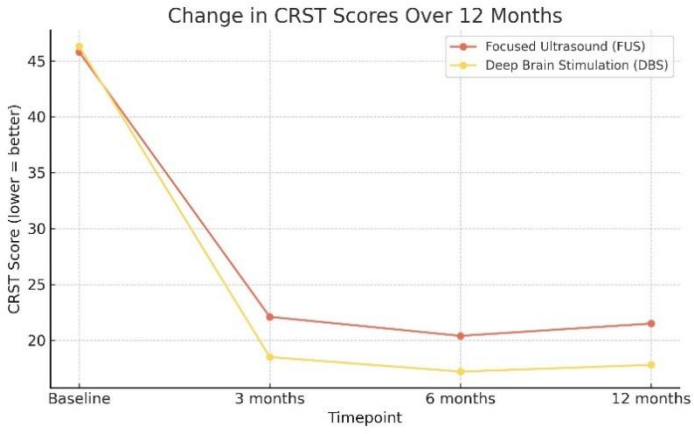


*Figure 2 Change in CRST Scores Over 12 Months*

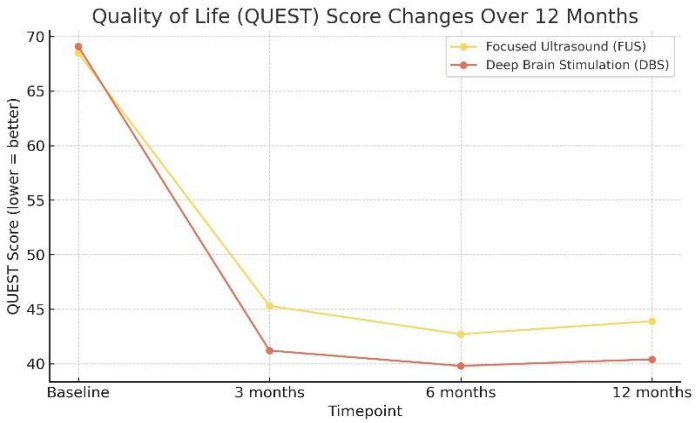


*Figure 2 Quality of Life (QUEST) Score Changes Over 12 Months*

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## DISCUSSION

The results of this trial showed clear improvements in tremor severity and quality of life in both focused ultrasound (FUS) thalamotomy and deep brain stimulation (DBS) groups, aligning with recent literature and providing evidence that both surgical modalities remain effective for medication-refractory essential tremor. The significant reduction in tremor severity observed in each group at three, six, and twelve months reflects findings in large cohort and meta-analytic studies demonstrating sustained tremor control with MRgFUS across one-year follow-ups and beyond. Meta-analyses of MRgFUS trials have reported similar tremor amelioration, with improvement rates commonly exceeding 50% after one year, indicating durable efficacy of this non-invasive approach (15,16). The greater reduction in Clinical Rating Scale for Tremor (CRST) scores in the DBS group observed at later follow-up points is consistent with previous comparative analyses suggesting superior tremor control with DBS, particularly when bilateral stimulation is applied. Large comparative reviews have noted that while MRgFUS offers substantial benefit for unilateral tremor, bilateral DBS more consistently achieves superior overall tremor suppression (17). The interaction effects seen in repeated-measures analyses in this study lend support to these broader findings, physiologically consistent with the adjustable and chronic neuromodulatory nature of DBS, which may sustain greater suppression over time. Quality of life improvements, quantified through standardized measures such as the QUEST questionnaire, followed a parallel trajectory in both groups. The statistically significant enhancement in patient-reported quality of life seen here is well supported by prior clinical research in essential tremor populations, where MRgFUS and DBS both yield meaningful gains in functional capacity and daily living activities at intermediate follow-up durations (18,19). In some comparative population studies, patient-reported quality of life improvements were noted to be greater in MRgFUS cohorts; however, those analyses did not always differentiate between unilateral versus bilateral DBS, which complicates direct clinical comparisons (20). The adverse event profiles in the present trial further reflect established patterns described in the wider literature. FUS was associated with a higher proportion of transient sensory and balance disturbances, while DBS was linked to hardware-related complications such as infections and rare hemorrhagic events, mirroring adverse event trends reported in large clinical experiences (21).

Importantly, cognitive outcomes remained stable in both groups over the one-year period, an encouraging observation given concerns about potential long-term neurocognitive effects of ablative procedures. Continued monitoring beyond 12 months would be valuable to fully characterize these trajectories. This study's findings have implications for clinical surgical decision-making in essential tremor. The relative balance between tremor suppression and adverse event risk, particularly with regard to device-related complications in DBS versus neurologic side effects associated with ablative lesions, remains central to tailoring individual patient care. MRgFUS's non-invasiveness and lower perioperative burden make it an attractive option, especially for older patients or those with contraindications to more invasive procedures. Conversely, DBS's adjustable stimulation parameters and capacity for bilateral treatment suggest it remains optimal for patients with bilateral or more severe symptomatology (22). Strengths of this study include its randomized, controlled design and standardized outcome assessments, ensuring comparability of long-term efficacy and safety across both interventions. The prospective capture of standardized tremor ratings and quality of life metrics strengthens the validity of observed effects over time. However, limitations must be acknowledged. The sample size, while calculated to detect clinically meaningful differences, may underpower detection of less common adverse events or subtle cognitive changes. Additionally, the unilateral nature of MRgFUS treatment in this protocol limits direct extrapolation to bilateral approaches, which emerging evidence suggests may be both safe and effective when staged, though further study is required (23). Future research could explore bilateral MRgFUS strategies, extended follow-up beyond 12 months to assess durability and potential recurrence of tremor control, and patient-centered outcomes such as cost-effectiveness and caregiver burden. In summary, this trial reinforces that both MRgFUS thalamotomy and DBS offer substantial benefit for patients with medication-refractory essential tremor. While DBS demonstrated slightly greater long-term tremor suppression and quality of life improvements, FUS offered comparable efficacy with a favorable safety profile in the short term. These comparative insights contribute to nuanced, evidence-based surgical planning and highlight areas for future investigation to refine patient selection and optimize long-term outcomes.

## CONCLUSION

Both MR-guided focused ultrasound thalamotomy and deep brain stimulation demonstrated substantial and sustained improvement in tremor control and quality of life among patients with medication-refractory essential tremor. DBS offered marginally superior long-term efficacy, while FUS provided comparable outcomes with fewer serious or hardware-related complications. These findings support

individualized surgical decision-making, emphasizing FUS as a viable minimally invasive alternative and DBS as the preferred option for bilateral or more severe tremor cases in functional neurosurgical practice.

## AUTHOR CONTRIBUTIONS

| Author | Contribution |
|---|---|
| Muhamad Hammad Nasir* | Substantial Contribution to study design, analysis, acquisition of Data<br>Manuscript Writing<br>Has given Final Approval of the version to be published |
| Usama Mansoor* | Substantial Contribution to study design, acquisition and interpretation of Data<br>Critical Review and Manuscript Writing<br>Has given Final Approval of the version to be published |
| Nabil Ashraf Cheema | Substantial Contribution to acquisition and interpretation of Data<br>Has given Final Approval of the version to be published |
| Anjlee Shankar | Contributed to Data Collection and Analysis<br>Has given Final Approval of the version to be published |
| M. Azhar Arshad | Contributed to Data Collection and Analysis<br>Has given Final Approval of the version to be published |
| Bakhtawar Siddiq | Substantial Contribution to study design and Data Analysis<br>Has given Final Approval of the version to be published |
| Shaikh Khalid Muhammad | Contributed to study concept and Data collection<br>Has given Final Approval of the version to be published |
| Abdul Sami Shaikh | Writing - Review & Editing, Assistance with Data Curation |
| Akif Saeed Ch | Writing - Review & Editing, Assistance with Data Curation |

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