Cost-effectiveness analysis of MR-guided focused ultrasound thalamotomy for tremor-dominant Parkinson's disease

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OBJECTIVE The development of transcranial MR-guided focused ultrasound (MRgFUS) has revitalized the practice of lesioning procedures in functional neurosurgery. Previous health economic analysis found MRgFUS thalamotomy to be a cost-effective treatment for patients with essential tremor, supporting its reimbursement. With the publication of level I evidence in support of MRgFUS thalamotomy for patients with tremor-dominant Parkinson's disease (TDPD), the authors performed a health economic comparison between MRgFUS, deep brain stimulation (DBS), and medical therapy.

METHODS The authors used a decision tree model with rollback analysis and one-factor sensitivity analysis. Literature searches of MRgFUS thalamotomy and unilateral DBS of the ventrointermediate nucleus of the thalamus for TDPD were performed to determine the utility and probabilities for the model. Costs in Canadian dollars (CAD) were derived from the Schedule of Benefits and Fees in Ontario, Canada, and expert opinion on usage.

RESULTS MRgFUS was associated with an expected cost of \$14,831 CAD. Adding MRgFUS to continued medical therapy resulted in an incremental cost-effectiveness ratio of \$30,078 per quality-adjusted life year (QALY), which remained cost-effective under various scenarios in the sensitivity analysis. Comparing DBS to MRgFUS, while DBS did not achieve the willingness-to-pay threshold (\$56,503 per QALY) in the base case scenario, it did so under several scenarios in the sensitivity analysis.

CONCLUSIONS MRgFUS thalamotomy is a cost-effective treatment for patients with TDPD, particularly over continued medical therapy. While MRgFUS remains competitive with DBS, the cost-effectiveness advantage is less substantial. These results will help inform the integration of this technology in the healthcare system.

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KEYWORDS MR-guided focused ultrasound; MRgFUS; thalamotomy; tremor-dominant Parkinson's disease; cost-effectiveness; functional neurosurgery

PATIENTS with Parkinson's disease (PD) suffer from a variety of motor and nonmotor symptoms. For this common neurological disorder, the cardinal motor features are tremor, bradykinesia, rigidity, and postural instability. A subset of patients experiences predominantly tremor with earlier onset and slower disease progression, termed tremor-dominant PD (TDPD). In contrast to akinetic-rigid, postural instability, or intermediate subtypes,

TDPD is a relatively infrequent subtype within the PD population, with a reported prevalence as low as 7%.^{1–4} However, tremor in these patients may be more resistant to dopaminergic replacement therapy and thus potentially amenable to surgical strategies targeting the ventrointermediate nucleus (VIM) of the thalamus with deep brain stimulation (DBS) or lesioning.⁵

The development of transcranial MR-guided focused

ABBREVIATIONS DBS = deep brain stimulation; ICER = incremental cost-effectiveness ratio; MRgFUS = MR-guided focused ultrasound; PD = Parkinson's disease; QALY = quality-adjusted life year; TDPD = tremor-dominant PD; VIM = ventrointermediate nucleus.

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ultrasound (MRgFUS) has revitalized the practice of lesioning procedures in functional neurosurgery. Performed with the patient awake in an MRI scanner, MRgFUS allows for real-time clinical and radiological feedback. These features promise to render lesioning safer and more precise. MRgFUS has also gained popularity in the media and general public, given its minimally invasive nature.⁶ In a recent randomized controlled study, Bond et al. demonstrated unilateral MRgFUS thalamotomy to be more effective than sham for medically refractory TDPD.⁷ Given the numerous strains on today's healthcare system, another potential advantage is the economic value of MRgFUS compared to DBS. Previous health economic analysis found MRgFUS is more cost-effective than stereotactic radiosurgery and DBS for essential tremor, supporting its reimbursement.^{8,9} This comparison has not been evaluated for TDPD. This study aims to compare the cost-effectiveness of MRgFUS and medical therapy alone or DBS, to better inform the integration of this technology in the healthcare system.

Methods

Model Design

Figure 1 illustrates the decision-analysis tree used to compare unilateral MRgFUS thalamotomy to medical therapy alone and to unilateral VIM DBS for severe TDPD. The former comparison is relevant for patients averse to invasive procedures or those with highly advanced disease or comorbidities that prohibit general anesthesia. Complications subsequent to each strategy are categorized as minor (e.g., paresthesia and wound infection) or major (e.g., weakness, dysarthria, intracranial hemorrhage) (Table 1). We omitted transient complications (e.g., nausea, pin-site swelling) or complications that can be resolved with DBS parameter adjustments. The possibility of reoperation after DBS was modeled for cases of hardware malfunction or infection. Due to insufficient published data, we did not model reoperation after MRgFUS thalamotomy, although this is theoretically possible with tremor reemergence. Finally, the rates of perioperative death and long-term mortality were considered negligible.

Model Parameters

Table 1 summarizes the base case scenario parameters. Probabilities were derived from a systematic search of peer-reviewed literature concerning unilateral VIM DBS and MRgFUS thalamotomy for TDPD (Figs. S1 and S2). Studies not in English, those reporting singular cases, or those with follow-up less than 3 months were excluded. Table S1 tabulates the studies included and their results. Utility, a number from zero to one representing the preference for specific health-related outcomes of various complications, was also extracted from the literature (Table 2, Table S2). The utility for medically refractory TDPD is 0.65, mapped from the baseline Parkinson's Disease Questionnaire-39 (PDQ-39) score from the aforementioned randomized controlled study.⁷ The utility benefit from each strategy was interpolated from the weighted average improvement in tremor score. The probability and utility of complications were also calculated from weight-

ed averages. Finally, the utilities were discounted at a 1.5% yearly rate, as is standard in cost-effectiveness analysis.

Costs (in Canadian dollars) were derived from a combination of the Schedule of Benefits and Fees in Ontario, Canada, and expert opinion on medical resource usage, adjusted to Canadian dollar value in 2020. Costs for the interventions and subsequent complications are summarized in Tables 1 and 2, respectively, and further itemized in Tables S3 and S4. The total cost of MRgFUS thalamotomy was \$14,788, which is lower than the \$22,229 cost for VIM DBS. Assuming patients remain on medical therapy despite receiving surgery, medication costs (estimated \$1700 per year) apply across all strategies. Notably, we converted the upfront and maintenance cost of the MRgFUS device to per-case cost, accounting for the expected 10-year lifetime and volume of 3 cases per month for all indications.

Analysis

Quality-adjusted life year (QALY) integrates the value of a health outcome with time in years. The incremental cost-effectiveness ratio (ICER) is the additional cost per added benefit provided by one treatment strategy over another (e.g., $[\text{cost A} - \text{cost B}]/[\text{QALY A} - \text{QALY B}]$). A standard willingness-to-pay threshold of \$50,000 per QALY was used to assess cost-effectiveness from a societal perspective. A rollback analysis was implemented using the TreePlan add-in for Microsoft Excel 2016. We employed a time horizon of 3 years in the base case. Subsequently, we performed a one-factor sensitivity analysis, varying by 20% the cost of each strategy, the probability of reoperation after DBS, cost of reoperation, and probability of major complication. Given the relatively limited long-term data on MRgFUS, the time horizon was also varied between 2 and 4 years.

Results

A systematic search for studies investigating unilateral MRgFUS thermoablation or DBS of the VIM was performed, yielding 24 and 432 unique records, respectively (Figs. S1 and S2). After abstract and full-text screening by three authors, final extraction of data regarding efficacy and, where available, complications was performed on 4 MRgFUS and 9 DBS studies (Table S1).

MRgFUS was associated with an expected cost of \$14,831. Adding MRgFUS to continued medical therapy resulted in an ICER of \$30,078 per QALY, below the commonly cited willingness-to-pay threshold. This result suggests MRgFUS thalamotomy would be a cost-effective option for severe TDPD. In the sensitivity analysis, the time horizon was responsible for the most variability in the result and the probability of a major complication the least. All scenarios were considered cost-effective (Fig. 2A).

In the base case scenario comparing MRgFUS to DBS, DBS had a moderately higher QALY by 0.15 over 3 years. The expected cost was also higher by \$8726 (\$23,557 vs \$14,831). The expenses associated with DBS were incurred notably from the device and potential complications that might require reoperation or hardware replacement. The

FIG. 1. Cost-effectiveness analysis decision-tree model. Figure is available in color online only.

resulting ICER of DBS vs MRgFUS was \$56,503 per QALY, above the standard willingness-to-pay threshold, suggesting in this scenario that MRgFUS was more cost-effective. In our sensitivity analysis, MRgFUS remained competitive except in the extremes of these 4 variables: efficacy of MRgFUS, cost of DBS or MRgFUS, and time horizon (Fig. 2B). In the best-case scenario for DBS, at a cost of \$17,783 per case, the ICER was \$27,716 per QALY.

Discussion

In this study, we found unilateral MRgFUS thalamotomy is a cost-effective addition to medical therapy, a similar conclusion to that of previous reports on essential tremor. Furthermore, this result was robust to variations in model parameter and assumptions and would be relevant for reimbursement of MRgFUS.^{9,10} Notably, MRgFUS has several valuable advantages stemming from the proce-

dures' lack of incision or implant. These factors are particularly attractive to elderly patients with contraindications to invasive procedures or who live a long distance from a tertiary center.

MRgFUS was more cost-effective than DBS in the base case scenario. Our expected cost difference was similar to an evaluation conducted within the United States healthcare system (\$7313).⁹ However, the advantage for MRgFUS was lost when we took into account our uncertainty in several variables. For instance, many of the DBS studies were published prior to 2010. More recent advances in DBS techniques might translate into lower complication rates and cost savings. DBS offers flexibility in parameter adjustments, which may be associated with more optimal clinical benefit and the possibility to adjust settings as the disease progresses. DBS also currently offers the opportunity for bilateral treatment, whereas bilateral MRgFUS lesions will require investigation to establish

TABLE 1. Model parameters

Parameter	MRgFUS	DBS
Probability		
Minor complication	18.7%	3.7%
Major complication	6.8%	18.9%
Reoperation	NA	9%
Cost (CAD)		
Per case	\$14,788	\$22,229
Preoperative	\$1220	\$1220
Intraoperative	\$13,255	\$19,766
Postoperative	\$143	\$493
Follow-up	\$170	\$750
Reoperation	NA	\$12,837
Minor complication	\$94	\$212
Major complication	\$385	\$779
Utility		
Baseline	0.650	0.650
Added utility	0.209	0.261
Minor complication	0.820	0.880
Major complication	0.780	0.820
Reoperation	NA	0.915

CAD = Canadian dollars; NA = not assessed.
Probability refers to the chance of an occurrence after respective intervention, in reference to the model in Fig. 1. Utility is a number from zero to one representing the preference for specific health-related outcomes.

whether they are a safe option for TDPD patients. On the other hand, MRgFUS, which is a relatively nascent technology, will likely evolve to be less expensive and more effective as clinical experience improves. Finally, it is important to highlight that cost-effectiveness is one among many considerations, including any additional symptoms (e.g., any gait instability), medical comorbidities, and patient preference, that might sway the patient and clinician toward one strategy versus the other.

There are other strong arguments for moving toward minimally invasive technologies.¹¹ The rationale includes less trauma, decreased surgery-related complications such as infection, earlier recovery, and in many cases, higher precision with the aid of image guidance. Despite substantial start-up costs, the cost per MRgFUS case will only decrease with increased volumes and indications. Furthermore, other indirect cost savings may be considered. For example, by treating some patients out of the operating room, opportunities are created for other surgical cases.

There are several limitations to this study. First, our parameter estimates were based on heterogeneous literature consisting of mostly case series. The relevant investigations for DBS are relatively dated. Furthermore, a head-to-head study between MRgFUS and DBS is not available. Second, our model did not account for time-sensitive variables, such as the decline in tremor suppression over time, retreatment, and reoperation for internal pulse generator replacements. In studies with essential tremor, while the overall benefit from MRgFUS thalamotomy was still significant at 2 years and 4 years, the reemergence of tremor

TABLE 2. Breakdown of the probability, cost, and utility of minor and major complications

Complication	MRgFUS (%)	DBS (%)	Cost (CAD)	Utility
Minor				
Paresthesia	10.2	—	\$85	0.81
Dysarthria	1.7	—	\$185	0.82
Dysgeusia	6.8	—	\$85	0.83
Infection	—	2.9	\$220	0.90
Cognitive changes	—	0.8	\$185	0.81
Major				
Ataxia	1.7	3.8	\$385	0.89
Weakness	5.1	1.9	\$385	0.74
Intracerebral hematoma	—	2.5	\$885	0.75
Seizure	—	0.9	\$485	0.91
Cardiac ischemia	—	0.3	\$800	0.83
Deep vein thrombosis	—	0.3	\$5000	0.81
Device problem	—	9.2	\$885	0.82

— = not applicable.
Detailed referencing of the cost and utility values can be found in the Supplementary Materials.

is evident in some patients.^{12,13} Indeed, the clinical choices after tremor recurrence can be complex and require a good understanding of the reason for recurrence.

Finally, the restricted target population is an important consideration. The number of patients with medically refractory TDPD, who might be candidates for surgery, is limited. PD patients with intractable tremor and other symptoms well controlled by medications might also be considered for VIM lesioning. DBS of other targets such as the subthalamic nucleus and globus pallidus interna may be an option when TDPD patients who have undergone MRgFUS thalamotomy or VIM DBS develop additional symptoms with disease progression and transition into a different PD subtype.¹⁴ For PD patients with the akinetic-rigid subtype, the subthalamic nucleus and globus pallidus interna are more appropriate targets.¹⁵ Small cohorts of MRgFUS subthalamotomy and pallidotomy have shown promising safety and efficacy data (between 32% and 53% improvement in Movement Disorder Society–Unified Parkinson’s Disease Rating Scale motor score at 6 months),^{16,17} with larger controlled studies underway (NCT02347254 and NCT03964272). Whether MRgFUS will remain competitive with DBS for PD in these various scenarios will have to be addressed by more complex models and take into account these results.

Conclusions

MRgFUS thalamotomy is a cost-effective treatment for patients with TDPD, particularly over continued medical therapy with an ICER of \$30,078 per QALY. While MRgFUS remains competitive with DBS, the cost-effectiveness advantage is less substantial. These results will help inform the integration of this emerging technology in the healthcare system.

FIG. 2. Tornado plots showing sensitivity analysis for MRgFUS versus medical therapy (A) and DBS versus MRgFUS (B).

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Disclosures

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Conception and design: Lipsman, Meng, Suppiah, Mithani. Acquisition of data: Meng, Pople, Bigioni, Li, Suppiah, Mithani. Analysis and interpretation of data: Meng, Pople, SK Kalia, Davidson, Bigioni, Li, Mithani, Schwartz, Hamani. Drafting the article: Meng, Pople, Davidson, Li, Hamani. Critically revising the article: Lipsman, Meng, Pople, SK Kalia, LV Kalia, Davidson, Suppiah, Mithani, Scantlebury, Schwartz, Hamani. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Lipsman. Statistical analysis: Meng, Davidson, Mithani. Administrative/technical/material support: Pople, Bigioni, Scantlebury. Study supervision: Lipsman.

Supplemental Information

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