Gamma Knife Thalamotomy for Disabling Tremor

A Blinded Evaluation

Shen-Yang Lim, MBBS, MD, FRACP; Mojgan Hodaie, MD, MSc, FRCSC; Melanie Fallis, RN; Yu-Yan Poon, RN; Filomena Mazzella, RN; Elena Moro, MD, PhD

Background: Gamma knife thalamotomy (GKT) has been used as a therapeutic option for patients with disabling tremor refractory to medications. Impressive improvement of tremor has been reported in the neurological literature, but the reliability of such data has been questioned.

Objective: To prospectively evaluate clinical outcomes after GKT for disabling tremor with blinded assessments.

Design: Prospective study with blinded independent neurologic evaluations.

Setting: University hospital.

Patients: Consecutive patients who underwent unilateral GKT for essential tremor and Parkinson disease tremor at our center. These patients were unwilling or deemed unsuitable candidates for deep brain stimulation or other surgical procedures.

Interventions: Unilateral GKT and regular follow-up evaluations for up to 30 months, with blinded video evaluations by a movement disorders neurologist.

Main Outcome Measures: Clinical outcomes, as measured by the Fahn-Tolosa-Marin Tremor Rating Scale and activities of daily living scores, and incidence of adverse events.

Results: From September 1, 2006, to November 30, 2008, 18 patients underwent unilateral GKT for essential tremor and Parkinson disease tremor at our center. Videos for 14 patients (11 with essential tremor, 3 with Parkinson disease tremor) with at least 6 months’ postoperative follow-up were available for analysis (mean [SD] follow-up duration, 19.2 [7.3] months; range, 7-30 months). The Fahn-Tolosa-Marin Tremor Rating Scale activities of daily living scores improved significantly after GKT (P = .03; median and mean change scores, 2.5 and 2.7 points, respectively [range of scale was 0-27]), but there was no significant improvement in other Fahn-Tolosa-Marin Tremor Rating Scale items (P = .53 for resting tremor, P = .24 for postural tremor, P = .62 for action tremor, P = .40 for drawing, P > .99 for pouring water, P = .89 for head tremor). Handwriting and Unified Parkinson’s Disease Rating Scale activities of daily living scores tended to improve (P = .07 and .11, respectively). Three patients developed delayed neurologic adverse events.

Conclusions: Overall, we found that GKT provided only modest antitremor efficacy. Of the 2 patients with essential tremor who experienced marked improvement in tremor, 1 subsequently experienced a serious adverse event. Further prospective studies with careful neurologic evaluation of outcomes are necessary before GKT can be recommended for disabling tremor on a routine clinical basis.

Arch Neurol. 2010;67(5):584-588
Toronto Western Hospital. Complications of treatment were also evaluated.

**METHODS**

**PATIENTS**

Eighteen patients (15 with ET, 3 with PD tremor) underwent GKT for ET or PD tremor at the Toronto Western Hospital from September 1, 2006, to November 30, 2008. Inclusion criteria were as follows: (1) presence of disabling resting and/or postural and/or action tremor in at least 1 limb; and (2) being unwilling or deemed unsuitable to undergo stereotactic radiofrequency lesioning (thalamotomy) or thalamic ventralis intermedius nucleus deep brain stimulation (DBS) surgery. These surgical procedures were typically not recommended because of the presence of severe comorbidities such as prior stroke, coronary artery disease, coagulopathy, uncontrolled diabetes, or active malignant neoplasm. All patients gave informed written consent for participation in the study.

**TREMOR EVALUATION**

Pre-GKT and post-GKT data were collected prospectively (within 1-2 weeks before surgery and at approximately 6, 12, and 24 months after surgery). Upper limb and head tremor were graded by an independent movement disorders neurologist not involved in the primary care of the patients (S.-Y.L.) according to the Fahn-Tolosa-Marin Tremor Rating Scale (TRS)\(^9\) using blinded pretreatment and posttreatment video recordings. Videos were recorded by research nurses (M.F., Y.-Y.P., F.M., or Sherry Kotusiewicz, RN); the video segments were then randomized (M.F. and Ms Kotusiewicz) (for example, videos 29, 1, 10, and 35 represented the baseline and 4-, 20-, and 30-month recordings, respectively, for patient 1). These were presented on compact disc to one of us (S.-Y.L.), who performed the evaluations in private over several sessions. The TRS items, although a trend toward improvement for handwriting, were 4 vs 1, respectively; hand function scores were 4 vs 1, respectively; and pouring scores were 4 vs 1, respectively (pouring). The other patient (patient 8) improved similarly (at baseline, 7 months, and 13 months, postural tremor scores were 4 vs 1, respectively; action/intention tremor scores were 4 vs 1, respectively (handwriting), 11 vs 3, respectively (drawing), and 4 vs 1, respectively (pouring). The other patient (patient 8) improved similarly (at baseline, 7 months, and 13 months, postural tremor scores were 3, 2, and 1, respectively; action tremor scores were 1, 1, and 1, respectively; handwriting scores were 2, 2, and 0, respectively; drawing scores were 9, 4, and 3, respectively; and pouring scores were 2, 3, and 1, respectively); however, this patient experienced a serious adverse effect 14 months after GKT (see later). One patient with PD tremor (patient 12) experienced abolition of resting tremor (score of 3 at base-
line, 2 at 7 months, and 0 at 18 months), but this effect did not appear to be sustained (score of 3 again at 26 months). Because of lack of tremor suppression from GKT, 2 patients (patients 2 and 6) subsequently underwent open surgery (ventralis intermedius DBS and thalamotomy, respectively) on the same side as the GKT (31 and 24 months after GKT, respectively). At 4 months’ post-DBS follow-up, patient 2 demonstrated an 80% reduction (from a score of 20 to 4) in the combined TRS score for the contralateral upper limb (comparing off vs on stimulation conditions using blinded video recordings) with a corresponding improvement of the TRS ADL score to 7 (this was 20 prior to DBS surgery). Patient 6 has not been formally evaluated after thalamotomy.

Three patients developed delayed neurologic adverse events, which were mild in 2 patients and serious in 1. Patient 8 developed extensive edema surrounding the thalamic lesion (2.3 cm, extending down into the midbrain and up into the corona radiata, with compression of the left lateral ventricle) and subsequently (14 months after GKT) developed a thalamic hemorrhage at the lesion site (Figure). The bleeding occurred in the context of the pa-

### Table 1. Patient Demographic Characteristics and Raw Scores of Tremor Evaluations at Baseline and During Follow-up Visits

<table>
<thead>
<tr>
<th>Patient No./Sex/ Age, y</th>
<th>Raw Score of Tremor Evaluation</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Head Tremor</th>
<th>TRS ADL or UPDRS Part II</th>
</tr>
</thead>
<tbody>
<tr>
<td>No./Blinded Video Evaluations, mo After GKT</td>
<td>Resting Tremora</td>
<td>Postural Tremorb</td>
<td>Action Tremorb</td>
<td>Handwritingb</td>
<td>Drawingc</td>
<td>Pouring Waterd</td>
<td>Combinedd</td>
<td></td>
</tr>
<tr>
<td>1/M/78 0/4/20/30</td>
<td>0/0/1</td>
<td>2/3/1</td>
<td>2/3/2</td>
<td>2/3/4</td>
<td>6/9/5</td>
<td>4/4/4</td>
<td>16/22/16</td>
<td>0/0/0</td>
</tr>
<tr>
<td>2/F/76 0/6/12/26</td>
<td>2/1/2</td>
<td>2/3/3</td>
<td>2/3/3</td>
<td>4/4/3</td>
<td>9/9/9</td>
<td>4/4/3</td>
<td>23/22/24</td>
<td>1/0/0</td>
</tr>
<tr>
<td>4/M/82 0/7/19/24</td>
<td>1/0/0</td>
<td>2/2/2</td>
<td>2/1/1</td>
<td>0/0/0</td>
<td>4/3/6</td>
<td>2/2/3</td>
<td>11/8/12</td>
<td>1/0/1</td>
</tr>
<tr>
<td>5/M/75 0/6/12/24</td>
<td>2/0/1</td>
<td>4/3/1</td>
<td>4/3/2</td>
<td>4/2/1</td>
<td>11/6/6</td>
<td>4/4/2</td>
<td>29/18/30</td>
<td>3/3/3</td>
</tr>
<tr>
<td>6/M/68 0/3/11/24</td>
<td>1/0/0</td>
<td>3/2/3</td>
<td>4/2/4</td>
<td>4/2/3</td>
<td>12/9/9</td>
<td>4/3/9</td>
<td>28/15/24</td>
<td>0/0/0</td>
</tr>
<tr>
<td>7/M/83 0/7/18</td>
<td>1/1/1</td>
<td>3/3</td>
<td>2/3</td>
<td>4/4</td>
<td>12/12</td>
<td>3/4</td>
<td>25/27/28</td>
<td>2/2/2</td>
</tr>
<tr>
<td>8/M/82 0/7/13</td>
<td>0/0/0</td>
<td>3/2</td>
<td>1/1</td>
<td>2/0</td>
<td>9/4/3</td>
<td>2/3</td>
<td>17/12/6</td>
<td>0/1/0</td>
</tr>
<tr>
<td>9/M/64 0/6/13</td>
<td>0/0</td>
<td>2/1</td>
<td>3/2</td>
<td>3/2</td>
<td>9/10</td>
<td>3/3</td>
<td>20/18/16</td>
<td>2/2</td>
</tr>
<tr>
<td>10/M/78 0/9</td>
<td>0</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>12/12</td>
<td>4/4</td>
<td>28/28</td>
<td>1/2</td>
</tr>
<tr>
<td>11/M/76 0/7</td>
<td>2/3</td>
<td>3/3</td>
<td>3/3</td>
<td>2/3</td>
<td>7/9</td>
<td>3/4</td>
<td>20/25</td>
<td>3/0</td>
</tr>
<tr>
<td>12/M/70f 0/7/18/26</td>
<td>3/2/0</td>
<td>0/0/0</td>
<td>0/0/0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0/1/2</td>
</tr>
<tr>
<td>13/M/82f 0/9/18</td>
<td>4/3/4</td>
<td>3/2/3</td>
<td>2/2/2</td>
<td>0/0/0</td>
<td>9/4/3</td>
<td>2/3</td>
<td>17/12/6</td>
<td>0/1/0</td>
</tr>
<tr>
<td>14/M/69f 0/12/43</td>
<td>4/3</td>
<td>2/1</td>
<td>2/0</td>
<td>0/0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0/2</td>
</tr>
</tbody>
</table>

Abbreviations: ADL, activities of daily living; GKT, gamma knife thalamotomy; NA, not available; TRS, Fahn-Tolosa-Marin Tremor Rating Scale; UPDRS, Unified Parkinson’s Disease Rating Scale.

*Refers to the upper limb contralateral to the GKT.

*Possible scores range from 0 to 4.

*Possible scores range from 0 to 12.

Combined indicates the total score for resting tremor, postural tremor, action tremor, handwriting, drawing, and pouring water; possible scores range from 0 to 32.

*Possible scores range from 3 to 27 for the TRS ADL or from 0 to 32 for the UPDRS part II.

*Patients with Parkinson disease tremor (all other patients had essential tremor).

### Table 2. TRS Tremor, TRS Activities of Daily Living, and UPDRS Part II Scores at Last Follow-up Compared With Baseline

<table>
<thead>
<tr>
<th>TRS Item</th>
<th>Evaluable Subjects, No.</th>
<th>Score, Mean (SD)</th>
<th>P Value, Wilcoxon Signed Rank Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRS ADLd</td>
<td>10 with ET</td>
<td>19.7 (4.2)</td>
<td>12.3 (2.5)</td>
</tr>
<tr>
<td>UPDRS part IIe</td>
<td>3 with PD tremor</td>
<td>16.0 (4.0)</td>
<td>16.0 (4.0)</td>
</tr>
</tbody>
</table>

Abbreviations: ADL, activities of daily living; ET, essential tremor; GKT, gamma knife thalamotomy; PD, Parkinson disease; TRS, Fahn-Tolosa-Marin Tremor Rating Scale; UPDRS, Unified Parkinson’s Disease Rating Scale.

*Possible scores range from 0 to 4.

*Possible scores range from 0 to 12.

*Possible scores range from 0 to 32.

*Possible scores range from 0 to 27.

*Possible scores range from 0 to 52.
tient receiving warfarin sodium for chronic atrial fibrillation (the international normalized ratio was 1.8 at the time of presentation). This was associated with speech difficulty and right hemiparesis, and the patient was hospitalized for several weeks. Patient 4 had mild (nondisabling) lip and finger numbness contralateral to the thalamic lesion at 19 months, as did patient 7 at 18 months.

**COMMENT**

Patients underwent GKT because they were unwilling or deemed unsuitable candidates for DBS or other surgical procedures such as conventional thalamotomy. Using blinded assessments and standardized scales, we found a significant improvement only in TRS ADL scores after unilateral GKT; however, the degree of this improvement (median, 2.5 points [range of scale was 0-27]) appeared to be modest and less than what is typically observed with neuromodulation. In the 3 patients with PD tremor, ADL (measured by the Unified Parkinson’s Disease Rating Scale part II, which ranges from scores of 0-52) improved to a similar degree (4, 5, and 2 points). A key point is that the improvement was seen with significant delay, typically 6 to 12 months after the procedure. We did not observe any other significant benefit after a mean (SD) follow-up period of 19.2 (7.3) months (range, 7-30 months). Marked and sustained improvement of tremor was observed in only 2 patients (with ET), with 1 of these patients subsequently developing a delayed and serious neurologic complication.

Our findings contrast with other studies reporting marked improvement of resting, postural, and action tremor after GKT. The largest of these series reported on the combined experience at 2 gamma knife radiosurgery centers, but the reliability of their data—even though evaluations were stated to be blinded—has been questioned by others. To our knowledge, no other study has assessed the effectiveness of GKT using physician-blinded assessments or in terms of the effect of tremor on ADL as measured by validated scales. For example, a recent series of ET cases reported tremor improvement in 90% of patients, with 50% of patients showing no or only slight tremor after GKT. However, in this study, assessments were performed “during follow-up neurosurgical assessments . . . by the clinic staff” (it was not stated whether they were adequately trained to perform the evaluations) using only a limited number of TRS items (action tremor and handwriting). It is worthwhile to note, in this context, that the recent major studies of DBS have had to endure stringent standards to prove efficacy and safety. These studies were multicentered, followed patients for up to 5 years, used evaluations by neurologists blinded to treatment allocation, reported outcomes using validated scales (including the effect of interventions on ADL and quality of life), and provided comprehensive reporting of adverse events. It could be argued that a similar degree of rigor should be applied to all modern functional neurosurgical treatments, including gamma knife radiosurgery.

There are several possible reasons for the observed lack of major benefit after GKT. In functional neurosurgery for movement disorders, targeting must be highly accurate to produce optimal outcomes. However, GKT relies only on anatomical targeting using brain magnetic resonance imaging, which may not be as accurate as intraoperative electrophysiological mapping of the target site. Another limiting factor may relate to the unpredictable tissue response to ionizing radiation. Thus, in some cases lesions may be smaller than expected, and in other cases lesions may spread into adjacent structures such as the internal capsule to cause serious adverse effects. In line with this, we observed a wide range in lesion volume despite only a 10-Gy (to convert to rad, multiply by 100) variation in the dose of radiation delivered. One report found significantly better tremor reduction in patients given a high dose (range, 140-165 Gy; mean, 160 Gy).
compared with a low dose (range, 110-135 Gy; mean, 120 Gy). Friehs et al13 suggested that larger-than-expected lesions may be produced by doses of radiation in excess of 160 Gy and when more than 1 isocenter is used; however, this does not apply in our case because our total dose did not exceed 140 Gy and a single 4-mm collimator was used for all cases. Nevertheless, 1 serious adverse event has occurred so far, in a patient who received 140 Gy. Importantly, this complication was only observed 14 months after GKT, again emphasizing the need for long-term follow-up.7 Our incidence of serious adverse reaction was 1 in 17 cases (6%), which is comparable to that reported by other investigators.1

The principal limitation of this study is the small sample size. In addition, while homogeneity of assessment is likely to be improved by a single-rater method, it could be argued that using multiple raters may better safeguard against bias. It should be acknowledged that although video segments were blinded to operative status and randomized, the assessing neurologist (S.-Y.L.) was aware that the videos were of patients from the gamma knife program.

In conclusion, overall we found that the primary anti-tremor benefit of GKT was in reduction of ADL impairment; however, we did not observe widespread anti-tremor benefit. One patient experienced a serious adverse event. Further prospective studies with careful neurologic evaluation of outcomes are necessary before unilateral GKT can be recommended for disabling tremor on a routine clinical basis.

Accepted for Publication: November 23, 2009.
Correspondence: Elena Moro, MD, PhD, Movement Disorders Centre, McL 7-402, Toronto Western Hospital, 399 Bathurst St, Toronto, ON M5T 2S8, Canada (elena.moro@uhn.on.ca).

Author Contributions: Drs Lim and Moro had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Lim, Hodaie, and Moro. Acquisition of data: Lim, Hodaie, Fallis, Poon, Mazzella, and Moro. Analysis and interpretation of data: Lim, Hodaie, and Moro. Drafting of the manuscript: Lim. Critical revision of the manuscript for important intellectual content: Lim, Hodaie, Fallis, Poon, Mazzella, and Moro. Administrative, technical, and material support: Fallis, Poon, Mazzella, and Moro. Study supervision: Moro.

Financial Disclosure: Dr Moro has occasionally received honoraria from Medtronic for consulting services and lecturing.

Additional Contributions: Sherry Kotusiewicz, RN, assisted with videotaping patients and organizing data.

REFERENCES

Sign Up for Alerts—It’s Free! Archives of Neurology offers the ability to automatically receive the table of contents of Archives when it is published online. This also allows you to link to individual articles and view the abstract. It makes keeping up-to-date even easier! Go to http://pubs.ama-assn.org/misc/alerts.dtl to sign up for this free service.