Introduction

Tremor is the most common movement disorder, with more than five million Americans affected.\(^1\) Tremor reduces overall quality of life, most notably by impairing employment, daily tasks, and taking a psychological toll.\(^2\) Unfortunately, many patients do not respond to medical therapy.\(^3\) Deep-brain stimulation (DBS) and radiofrequency thalamotomy (RFT) are invasive procedures that ablate the ventralis intermedius (VIM) nucleus to relieve contralateral tremor.\(^4\) Both DBS and RFT are associated with morbidity and potential mortality.\(^1\) Stereotactic radiosurgery is an important non-invasive treatment for contralateral tremor relief and control in elderly and those considered high risk for DBS and RFT. Previous studies of gamma knife thalamotomy (GKT) for tremor indicate a clinical improvement in the range of 60-90%.\(^4,5,6\)

The purpose of this study is to further analyze the safety and effectiveness of GKT for a large cohort of patients afflicted with tremor. Our hypothesis is that GKT is a safe and effective treatment for the elderly or those not suitable for invasive procedures. We believe that if we can collect 200 or more patients from participating centers, this can become a powerful IGKRF study.

Methods

Patient Selection

The investigators will review the medical and imaging records of all eligible patients who underwent GKT for essential tremor (ET), Parkinson’s disease (PD) tremor, or multiple sclerosis (MS)-related tremor at participating IGKRF centers. All parameters listed in the attached excel sheet will be collected. The Fahn-Tolosa-Marin clinical tremor rating scale will be used to score tremor, handwriting, drawing, and ability to drink before and after GKT.\(^7\)
Statistical Analysis

The Wilcoxon signed rank test will be used to determine statistical significance for each FTM value (tremor, handwriting, drawing, and drinking) pre and post-GKT. Kaplan-Meier analysis will be used to determine the onset of tremor relief, categorized by tremor type. Patients without followup, or those that died (non-GKT related) before follow-up will be censored. For Kaplan-Meier analysis, the log-rank (Mantel-Cox), Breslow, and Tarone-Ware will used to determine statistical significance among tremor types. Multivariate analysis, with fixed factor (tremor type) will be used to determine the statistical significance of covariates (years of tremor, age at treatment, sex, time to followup, GKT isodose, GKT max. dose, GKT marg. Dose, and GKT target volume) to the dependent variables (clinical benefit, tremor recurrence, and complications). A p-value of 0.05 will be used to determine statistical significance.

Discussion

For nearly half a century, treatment of tremor has been surgical targeting the VIM nucleus of the thalamus, with patients of most tremor subsets experiencing some level of tremor relief. While DBS is the most common treatment for ET or PD, long term relief for MS-related tremor is less apparent. RFT is another option, sometimes performed in instances where DBS may not be financially feasible. While RFT has the ability to confirm the target site intraoperatively and slowly grow the lesion size over time, high complication rates are noted along with possible repeat procedures for sustained tremor relief.

The results of a literature review of 16 GKT studies for tremor indicated improvement in a median 87.5% (range, 0% to 100%) of patients. A previous report in 2010 noted improvement in a median 92% (range, 81-100%). We will also assess outcome of bilateral procedures. In a review of the literature, 2 out of 3 deaths directly attributable to radiosurgery had bilateral thalamotomy. In another study of ET, the authors present the results of a first and second GKT (bilateral) in 42 patients. For the first procedure, they note mean drawing scores 3.5 ± 0.7 and 1.4 ± 1.3 (p>0.0001), before and after GKT, respectively. For the first procedure they also note mean writing scores 3.0 ± 1.4 and 1.3 ± 1.2 (p>0.0001), before and after GKT, respectively. For the second procedure, they note mean drawing scores 3.1 ± 1.0 and 1.0 ± 0.9 (p<0.0001), before and after GKT, respectively. We will also evaluate the recurrence rate and factors associated with tremor recurrence after GKT. It is noted in literature that long term tremor relief may be less than initial benefit. Specifically, long-term results of tremor relief may range from 68.7 to 93%. Followup for up to 10 years, shows that as many as 50% of patients may return to pre-GKT levels. In a previous review of 14 articles, the initial benefit of GKT for MS-related tremor may be greater than 75%, with long term benefit for 50-73%.

While we believe GKT to be a safe and effective treatment option for patients with tremor, there are some notable criticisms. One such criticism is the lack of
electrophysiological information to verify the target site intraoperatively. Additionally, patients typically wait 1-4 months post-GKT to experience the onset of tremor relief. However, we believe there are three main benefits of GKT. First, GKT is especially attractive for patients who are at high risk of morbidity and possible mortality from invasive procedures (DBS and RFT). These patients include the elderly (age greater than 80 years) and those with simultaneous medical morbidities, including anticoagulant therapy, respiratory, or cardiac disease. Secondly, DBS, an invasive procedure, has a high cost over time with replacement of electrodes and followup procedures. We are in agreement that if GKT produces results similar to DBS, then GKT is preferable. Finally, GKT provides radiation that extends past the 50% isodose line, with a positive effect on the kinesthetic cells within the thalamus (without cell death), through tissue destruction and physiologic alteration of the tremor region. This peripheral effect, which has been extensively studied in primates, may allow for a larger treatment volume and robust maintenance due to radiation, in comparison to RFT.

References:


