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Unilateral gamma knife thalamotomy for tremor safety and efficacy in multimodal assessment: a prospective case-control study with two-year follow-up

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ABSTRACT

Introduction. Unilateral gamma knife thalamotomy (GKT) is a treatment option for pharmacoresistant tremor of various aetiologies. There have been to date no randomised controlled trials performed to assess its safety and efficacy. Our aim was to summarise a two-year multimodal observation of patients with tremor caused by Parkinson's Disease (PD) or essential tremor (ET).

Material and methods. 23 patients with PD (n = 12) or ET (n = 11) were included. They underwent assessments before, V0 (n = 23), and 12 months, V12 (n = 23), and 24 months, V24 (n = 15), after unilateral GKT. Patients were assessed with psychological tests and acoustic voice analysis. Tremor assessment was performed with a digitising table using the Fahn-Tolosa-Marin rating scale (FTMRS). The Unified Parkinson's Disease rating scale part III (UPDRS-III) was also used in the PD group. Gait and balance was assessed using clinical tests, stabilometric platform, and treadmill.

Results. No side effects were observed in a two-year follow-up. There was no notable deterioration observed in the patients' psychological evaluation, speech, or assessment of gait and balance. The scores were significantly lower (p = 0.01) in parts A and B of FTMRS one year after GKT. In post hoc analysis, the scores did not differ significantly between V0 and V24. In FTMRS part C (activities of daily living), no significant change was observed. There was no significant difference in total UPDRS part III score or in score of UPDRS part III domains 3 and 4 ('tremor at rest' and 'action and postural tremor of hands') between measurements.

Conclusions. UGKT may be a safe treatment modality if performed in an experienced centre. Tremor reduction may diminish over time, and UGKT did not lead to cognitive, gait or speech deterioration in a long-term observation.

Keywords: gamma knife thalamotomy, tremor, essential tremor, Parkinson's Disease

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Introduction

Tremor is the most frequent movement disorder worldwide [1]. Essential tremor (ET) is the most common cause of tremor, affecting c.0.9% of the global population [2]. Parkinson's Disease (PD) is another common cause of tremor. Tremor severity is markedly correlated with reduced quality of life [3]. Pharmacotherapy is the first line of treatment in both PD and ET. In PD, this includes mainly dopaminergic agents [4]. Anticholinergic drugs are also effective in tremor management, but are currently less commonly used due to their side effects, especially their negative effect on cognition [5]. Unfortunately, tremor in PD may not respond to dopaminergic treatment or may require higher doses of levodopa to stop. High levodopa doses can trigger orthostatic hypotension, dyskinesia and/or psychotic symptoms [6]. Similarly, in ET, pharmacotherapy is usually the first line of choice [7]. The agents with the highest evidence of efficacy according to the Movement Disorders Society (MDS) guidelines include propranolol, primidone and topiramate [8]. These can, however, lead to severe side effects that are unacceptable for some patients. These include bradycardia, hypotension, impotence, and depression during treatment with propranolol [9]. Primidone often causes sedation, nausea, dizziness, and disequilibrium [10]. Botulinum toxin has also been assessed in hand tremor in ET, with no significant effect [11].

Pharmacotherapy of tremor can therefore sometimes be ineffective or burdensome for patients. In such cases, surgical treatment is considered. Unilateral thalamotomy has been recognised as a safe and efficient method of treating pharmaco-resistant tremor for over 30 years. Neurosurgical treatment of tremor was initially performed using classical incisional methods requiring a hospital stay. In 1951, Leksell introduced the idea of closed-cranium single-session irradiation of a precisely defined intracranial target [12, 13]. Nowadays, the lesion can be treated with non-invasive access using stereotactic radiosurgery (SRS) methods such as gamma knife (GK) [14]. Magnetic resonance-guided focused ultrasound (MRgFUS) is a safe and swiftly developing new option [15, 16]. Stereotactic radiation or sonication targets the thalamic ventro-intermediate nucleus (VIM). Deep brain stimulation (DBS) of the VIM is another commonly used modality in the treatment of tremor [17].

The GK procedure uses isocentric gamma radiation beams from various angles which focus on the targeted area. Hence, a high dose of radiation goes to a specific region. Despite the fact that, after the mass introduction of DBS, many authors heralded the end of thalamotomy for tremor, the recent approval of MRgFUS thalamotomy has reignited the debate on the use of thalamotomy versus DBS for this indication. Nevertheless, MRgFUS remains unsuitable for some groups of patients due to limiting factors such as inappropriate skull density ratio. However, these patients can still benefit from gamma knife thalamotomy (GKT).

Unfortunately, to our best of our knowledge, no randomised controlled trial has assessed the efficacy of GKT in tremor. Therefore, this particular method of treating the thalamic lesion is not recommended in the current EAN/MDS guidelines on invasive therapies in the treatment of PD [18]. The guideline authors also indicate an inability to confirm the exact location and size of the lesion intraoperatively. So, the purpose of this paper was to summarise a long-term, multimodal assessment of patient clinical outcomes before and after GKT due to pharmacotherapy-resistant tremor in PD and ET patients.

Material and methods

This study was conducted at the Department of Neurology, Faculty of Health Sciences, Medical University of Warsaw, Poland between 2018 and 2022. The study was approved by the Bioethical Committee of the Medical University of Warsaw (KB/121/2018) and performed in accordance with the Declaration of Helsinki. All patients signed informed consent prior to participation in the study. The primary inclusion criterion was a diagnosis of ET or PD, with tremor as the predominant symptom. Only patients with tremor resistant to pharmacotherapy (due to insufficient control or to unacceptable side effects) were approached. Their tremor was causing them all a significant disturbance in the activities of daily living. Patients were informed as to the other options for treatment available (i.e. DBS, further modifications of pharmacotherapy).

Exclusion criteria included pregnancy and lactation, contraindications for performing magnetic resonance imaging, contraindications to radiosurgery (e.g. prior radiotherapy of the central nervous system), history of neurosurgical treatment for other causes, current treatment with DBS, or tremor well controlled with pharmacological treatment.

Eventually, 23 patients with PD (n = 12) or with ET (n = 11) with pharmaco-resistant tremor were included. The mean age was 64.3 ± 8.9 years, 17 were male and six female. They underwent assessments before, V0 (n = 23), and 12 months, V12 (n = 23), and 24 months, V24 (n = 15) after the thalamotomy. The PD group consisted of 12 patients with a mean age of 64.9 ± 7.8 and a mean disease duration of 6.0 years ± 3.4. The ET group consisted of 11 patients with a mean age of 62.7 ± 10.3, and a mean disease duration of 17.2 years ± 12.7.

There were 10 men in the ET group and seven in the PD group. The groups differed significantly in terms of disease duration ($p = 0.01$), but not in age. Due to the small number in each group, the majority of the patients' results were analysed jointly. GKT was performed unilaterally. Patients were able to choose the side of the lesion, usually choosing the dominant side where the tremor was more burdensome to their everyday activities.

GKT procedure

Unilateral GKT procedures were performed at the Warsaw Gamma Knife Centre. After stereotactic frame placement, contrast-enhanced 1 mm slice thickness axial T1, 3D, T2 FSE,

and FIESTA MR images were used for planning. A conformal plan was constructed in GammaPlan Software (Elekta, Sweden) using a 4 mm isocentre. The prescribed standard dose of 130 Gy was applied to all patients. All patients were operated on with a 192-source cobalt-60 Gamma Knife Perfexion unit. All imaging was performed in a GE Sigma HDxt 1.5T magnetic resonance imaging scanner and a 64-row GE computer tomography scanner.

Baseline and follow-up procedures

A test battery was performed at baseline, V0, and V12 (± 3 months) and V24 (± 3 months) after GKT. Imaging (1.5 T MRI) was performed at baseline and 12 months after the procedure to confirm the presence of the lesion and its location. Other tests comprised a psychological assessment, a gait assessment, and an automated speech assessment, as well as tremorometry with a dedicated device.

Clinical neurological examination included Unified Parkinson's Disease rating scale (UPDRS) part III, under both medicated ('ON') and unmedicated ('OFF') conditions (with a minimum of 12 hours PD medication washout), performed only on PD patients. A Fahn-Tolosa-Marin rating scale (FTMRS) assessment was performed both on PD and ET patients.

Tremorometry was performed both in the 'ON' and the 'OFF' state for PD patients, and without medications for ET patients. Only 'OFF' state measurements were used in the analysis, in order to limit the influence of dopaminergic treatment on tremor. Two-dimensional pen trajectories were recorded on a digitising tablet (Intuos series, Wacom, Vancouver, WA, USA) connected to a personal computer running custom-acquisition software [19]. During the examination, the patient traced along the template in a circle centred over the tablet's active area. The drawing direction was not imposed, and the drawing speed was roughly specified as "moderate". Each examination took c.100 seconds. Patients performed the task while seated and with the elbow of the examined arm unsupported. For further analysis, only the measurements from the hands contralateral to the thalamotomy side were considered. The acquired pen trajectories were processed to extract the oscillatory component of the drawing motion within the 2-12 Hz frequency band. The following metrics were calculated: a median peak-to-peak oscillation amplitude (med_pp), a median oscillation frequency (med_if), a median oscillation velocity (med_v), and a directional variability of oscillation (iqr_dphi), given as an interquartile range of the oscillation direction changes. Due to an observed, primarily linear, relationship between the instantaneous velocity and amplitudes of oscillation, a normalised oscillation velocity for 10 mm peak-to-peak amplitude (v_10_pp) was calculated using a linear regression model.

Gait and balance assessment included static posturography, equilibrium tests, and treadmill gait analysis. Posturography was performed on a TecnoBody Prokin M-line stabilometric platform with Prokin 3 software. Treadmill gait analysis was performed on a Zebris-type treadmill FDM-TDM with WinFDM-T software. Clinical balance tests included quantitative assessments with a Timed Up and Go test (TUG) and a tandem stance test (TST), as well as qualitative assessments comprising a tandem walking test (TWT) and a 180° tandem pivot test (TPT). The tests were always compared in the 'OFF' state in PD patients.

Psychological assessment included a Mini-Mental State Examination (MMSE), an executive clock drawing task (CLOX), Tower of London (ToL), Benton Judgement of Line Orientation (Benton JLO), Adverse Childhood Experience (ACE), Wechsler Adult Intelligence Scale (WAIS), Rey Auditory Verbal Learning Test (RAVLT), Boston Naming Test (BNT), and Beck's Depression Inventory (BDI). All psychological tests were performed in the 'ON' state in PD patients.

Speech assessment including acoustic voice analysis was performed on all subjects using dedicated DiagnoScope Specialist software (DiagNova Technologies). Each task was assessed completely automatically by the software. Speech examination was performed by a speech therapist (RK-T) as described previously [20]. Acoustic voice analysis parameters assessed included maximum phonation time, actual phonation time, no phonation coefficient, voice breaks coefficient, modulation depth frequency, modulation energy performance, and coefficient performance average.

Statistical analysis

Calculations were performed using GraphPad Prism v. 9.4.0 and Statistica 13.5 (StatSoft). One-way ANOVA for repeated measures was performed to compare the outcomes of baseline (V0), 12-month (V12), and 24-month (V24) assessments. Mixed model was used for data with missing values. Post hoc analysis was performed with Tukey's multiple comparisons test. Tremorometry results were analysed in R environment (v. 4.2.0) [21].

For tremor assessment with a digital tablet, metrics were compared between the specified visits. Logarithmic scales were used for med_pp, med_v, and v_10_pp due to the observed skewedness of the distributions of these metrics. These metrics were log-transformed prior to the hypothesis test. Wilcoxon signed-rank test for paired samples was used for all metrics. The calculated p-values were adjusted using the Benjamini-Hochberg correction method, accounting for 10 and five tests performed for comparison with, and without, the disease factor (i.e. ET/PD) respectively.

Results

Changes in UPDRS and FTMRS

The scores achieved in UPDRS part III and FTMRS are set out in Table 1. We observed significantly lower scores ($p = 0.01$) in parts A and B of FTMRS after GKT. In post hoc

Table 1. Results of clinical scales assessing tremor and parkinsonian symptoms during baseline, month 12 (V12) and month 24 (V24) visits compared to repeated measures ANOVA. UPDRS scale was only performed in patients diagnosed with Parkinson's Disease. P-value < 0.05 was considered significant. Significant differences marked with * and bold. FTMRS — Fahn-Tolosa-Marin rating scale; UPDRS — Unified Parkinson's Disease Rating Scale

Clinical scale	Baseline (points)	V12 (points)	V24 (points)	P-value
FTMRS part A	13.61*	9.59*	10.87	0.01
FTMRS part B	14.26*	10.50*	12.13	0.02
FTMRS part C	8.78	7.76	9.23	0.4
UPDRS part III	22.9	26.3	23.20	0.7
UPDRS part III tremor (items 3-4)	8.9	8.2	5.4	0.1

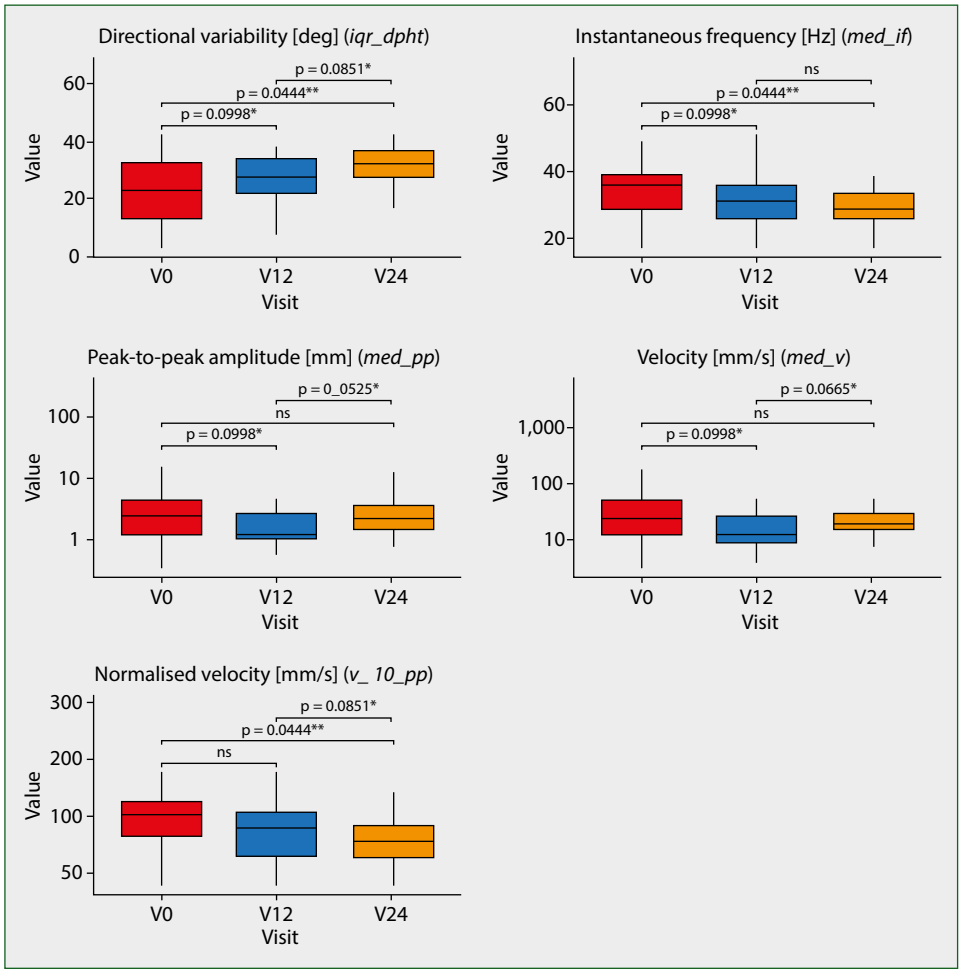

Figure 1. Tremorometry results: pairwise comparisons between visits V0, V12, and V24 (Wilcoxon paired test with FDR-adjusted p values; variables *med_pp*, *med_V*, and *v_10_pp* were log10-transformed before hypothesis test). Non-significant test results (p > 0.1) are marked as "ns". Group sizes: N(.) denotes number of patients in visit subgroup, and Np(.) denotes number of pairwise comparisons between given subgroups: N(V0) = 20, N(V12) = 20, N(V24) = 14, Np(V0V12) = 19, Np(V0V24) = 13, Np(V12V24) = 13

analysis, we did however observe that the effect was transient and did not differ significantly between V0 and V24. In FTMRS part C (activities of daily living), no significant change was observed. There was no significant difference in total UPDRS part III scores or in the score of UPDRS part III domains 3 and 4 ('tremor at rest' and 'action or postural tremor of hands') between measurements.

Tremorometry

The results of tremor measurements are set out in Figures 1 and 2. Pairwise comparisons between visits showed significant changes in the metrics (Fig. 1): the directional variability of oscillations (iqr_dphi) increased consistently between the baseline (V0), month 12 (V12), and month 24 (V24) visits; the motion frequency (med_if) lowered between visits V0 and

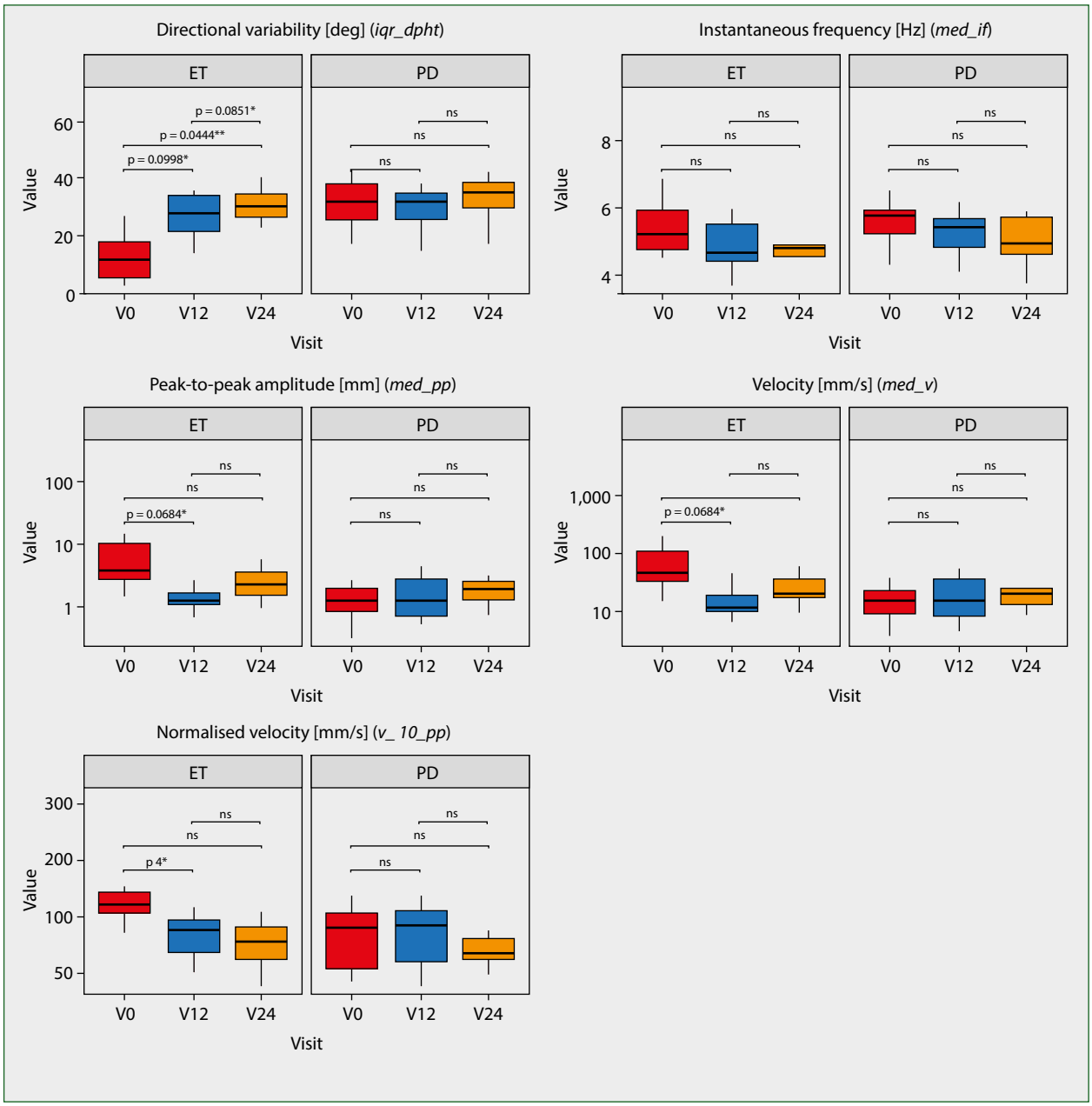

Figure 2. Tremorometry results in Parkinson's Disease (PD) and essential tremor (ET) patients: pairwise comparisons between visits V0, V12, and V24 within disease subgroups (Wilcoxon paired test with FDR-adjusted p values; variables *med_pp*, *med_V*, and *v_10_pp* were log10-transformed before hypothesis test). Non-significant test results ($p > 0.1$) are marked as "ns". Group sizes: N(.|d) denotes number of patients in visit subgroup "." for disease "d", and Np(.|d) denotes number of pairwise comparisons between given subgroups, for given disease: N(V0|ET) = 9, N(V0|PD) = 11, N(V12|ET) = 10, N(V12|PD) = 10, N(V24|ET) = 7, N(V24|PD) = 7, Np(V0V12|ET) = 9, Np(V0V12|PD) = 10, Np(V0V24|ET) = 6, Np(V0V24|PD) = 7, Np(V12V24|ET) = 7, Np(V12V24|PD) = 6

V12, showed no change between visits V12 and V24, but effectively remained lowered between visits V0 and V24; the amplitude (med_pp) and velocity (med_v) of oscillations decreased between visits V0 and V12, and subsequently increased between visits V12 and V24, finally yielding no significant difference between visits V0 and V24; the compound metric of normalised velocity (v_10_pp) did not change significantly between visits V0 and V12, decreased between visits V12 and V24, and finally decreased significantly in the longest observed timescale, i.e. between visits V0 and V24.

When the disease factor was included (ET / PD), significant differences ($p < 0.1$) were observed only for ET patients between the V0 and V12 visits, as set out in Figure 2. These included a rise of directional variability and decreases of amplitude, velocity, and normalised velocity. There were, however, no significant changes between visits V0 and V24, or between V12 and V24.

The observed changes in the amplitude and velocity of oscillations (metrics: med_pp, med_v) suggest a temporary suppression of a fast, largeamplitude, tremorous motion component between visits V0 and V12. However, this trend reverses during the next intervisit period and effectively vanishes when comparing V0 to V24. Some patients exhibited more pronounced progression (with both positive and negative trends) in the V12V24 period. It is worth noting that four of the observed parameters tended to show common relative-to-baseline majority trends at the two-year follow-up (i.e. an increase of directional variability, a decrease of frequency, and decreases of both velocities). This points to a patient-specific delay in response. The individual trajectories of tremorometry parameters of the patients are set out in Supplementary Table 1.

Psychological assessment and speech assessment

The results of subsequent psychological assessments of the patients are summarised in Supplementary Table 1. A transient (only significant between V0 and V12 in post hoc analysis) increase in CLOX-1 was observed ($p = 0.02$), with no difference in CLOX-2 (coping examiner's clock task). No other significant differences between the visits were observed. Voice acoustic parameters analysis revealed no significant changes in voice parameters between the visits, as shown in Supplementary Table 2.

Posturography

The results of assessments of gait and balance of patients before, and 12 and 24 months after, thalamotomy are set out in Supplementary Table 3. No significant differences between the visits were observed in the performance of the active tests or in balance and gait parameters in the results obtained from the treadmill and stabilometric platforms.

Discussion

The latest guidelines of the European Academy of Neurology and the European section of the MDS, published in 2022, do not recommend GKT in the treatment of tremor in PD. They indicate that no randomised controlled study on GKT has been published and that the procedure is at high risk of adverse events. The continuing evolution of the lesion long after the application of radiation can cause subsequent clinical side effects [18].

However, while our study was conducted before the publication of the new guidelines, we maintain that in our highly experienced centre this procedure is safe. We observed no patient in our cohort to suffer from any permanent complication from unilateral GKT over the following 24 months. The most commonly reported side effects were acceptable pain and discomfort during the application of the stereotaxic apparatus. In their systematic review of GKT, Campbell et al. reported that complications of GKT appear months to years post procedure, and most commonly consist of mild contralateral numbness and transient hemiparesis. Rarely, more severe complications have been reported, including dysphagia and death. Importantly, these were more frequent in rare cases of bilateral thalamotomy [14]. No such neurological symptoms were observed in our group.

Speech deterioration was not observed in our cohort. Cognition was also assessed thoroughly, with various tests assessing different domains. A meta-analysis of the influence of thalamotomy on tremor by Rohringer et al. indicated a small but significant decline in phonemic fluency after thalamotomy [22]. This observation was not confirmed in our study. That meta-analysis included, however, patients with not only PD and ET but also multiple sclerosis (MS), as well as involving different methods of thalamotomy (radiofrequency, GKT and MRgFUS). We speculate that MS patients may have different outcomes of the procedure due to their different backgrounds [23, 24]. Radiofrequency may be also more burdensome for patients due to its more invasive nature. We find the lack of cognitive deterioration encouraging, as it is also an important factor influencing falls and gait disturbances in PD patients [25, 26].

In our study, all patients received a standard dose of radiation of 130 Gy. We can only hypothesise that some of them could benefit from a higher dose in terms of tremor reduction, with a possibility of an increased risk of side effects. Young et al. concluded in their study that a small lesion size may be associated with a worse clinical effect [27]. Duma et al. reported a significant reduction in a "high dose" lesion group (radiation range 140–165 Gy, mean 160) versus "low dose" (range 110–135 Gy, mean 120) [28].Whereas nowadays the total dose usually does not exceed 120–140 Gy [14], in some initial studies it was reported to reach up to 200 Gy [29, 30]. This could also lead to more frequent side effects, which we did not observe in our study.

A review by Dallapiazza et al. comparing four modalities of tremor treatment i.e. DBS, GKT, FUS, and RF, actually indicated that despite being able to intraoperatively control the side effects, some of them (ataxia, paresthesias) may be more frequent in the FUS group than in the GKT group [31]. Some authors have included tractography to further decrease the risk of side effects during GKT, in particular damage to the internal capsule. Gomes et al. reported modifications of the coordination and gamma angle following diffusion tensor imaging tractography as a means of avoiding pyramidal tract lesioning and motor side effects [32].

There are several positive aspects of unilateral GKT compared to other procedures, as summarised by Niranjan et al. [33]. Firstly, GKT is a feasible treatment modality for patients who are at high risk of morbidity and possibly mortality from surgical procedures (i.e. DBS, radiofrequency treatment) involving burr holes. Secondly, while DBS requires frequent follow-up visits to optimise the settings and medications, GKT produces a lesion which provides a rather stable effect.

It may, therefore, be an option for patients unable to attend regular visits. The cost-effectiveness of the method should also be taken into consideration, as no changes of battery are required. This cost will be substantially reduced with the wider introduction of rechargeable DBS batteries. Ravikumar et al. performed an analysis of the cost and effectiveness of DBS, MRFuS and SRS. They found that MRgFUS is more costly than SRS, but also more effective [34].

Finally, GKT provides radiation that extends beyond the 50% isodose line, with a positive effect on the kinesthetic cells within the thalamus (without cell death). A typical radiosurgery response to GKT is a 4-5mm central necrotic lesion (in the highest-dose region), surrounded by a peripheral non-necrotic effect consisting of vascular changes and astrocytogliosis [33]. This effect is different from the changes induced by thermal lesions in MRgFUS. Therefore, the effect of GKT is likely a combination of central tissue destruction and peripheral physiological alteration of the tremor region [35]. Therefore, the clinical benefit from treatment may exceed the small lesion effect.

Our paper proves that in a highly experienced centre this method is safe and can be used in patients who could not be enrolled for MRgFUS thalamotomy. This aligns with other studies on GKT performed in larger groups of patients with a one-year follow up [36]. An interesting observation derived from our long-term observation was the reduction of the therapeutic effect on tremor after two years in some patients. Such partial 'rebounds' of tremor after GKT have been previously reported [37]. Similar results of increases of some tremor parameters were mentioned by Halpern et al. in a three-year observation of patients after MRgFUS thalamotomy [38]. The long-term increase of the motion directional variability, when accompanied by decrease of normalised motion velocity, may be seen as indicative of an ongoing confinement of hand micromovements. The analysis conducted within the separate PD and ET groups suggests that some of the abovementioned effects may be restricted to ET patients during the initial postintervention period (V0-V12). This may be due to the progression of PD-related neurodegeneration. This may be an important clinical observation, leading to changes in the choice of treatment options for patients with tremors of different aetiologies.

To the best of our knowledge, this has not been reported in previous studies. At the same time, some parameters of the tremor trajectory estimates indicate a patient-specific delay in response. Another evaluation with a three-year follow-up would be valuable in tracking further progression of these late responders.

The limitations of our study include a relatively small number of patients with a high dropout, partly caused by the long follow-up and by the coincidence with the COVID-19 pandemic. Raters were not blinded to patients' treatment status, and there was no placebo control with sham procedures performed in this study. Nevertheless, we included many standardised digital assessments such as digitising tablets to assess tremor, voice assessment with DiagnoScope software, and gait and balance assessment using a specialised stabilometric platform and treadmill. While these devices cannot replace blinded assessment with sham procedures, they provide unbiased and highly reproducible data uninfluenced by patient or neurologist preconceptions.

We also find it encouraging that the results of the FTMRS performed and the results of digital tremor assessment align. Taking into consideration a lack of evidence of the effect of treatment on GKT in RCTs, these results provide solid, reproducible outcomes. An important aspect of our study is the long follow-up, reaching 24 months in the majority of patients. Many studies have provided shorter follow-ups which may have been insufficient due to the evolving nature of GK-induced lesions. The recurrence of tremor observed in some patients after two years is an important observation, which should be taken into consideration when informing patients. An important limitation in the effect of GK procedures is the delay observed between radiation and lesion formation. Most authors have reported a delay in symptom relief after radiation, with a range of 1–4 months [31].

Conclusions

Unilateral GKT is a safe method of treatment. It did not lead to deteriorations of gait, balance, speech, mood, or cognition in patients with ET or PD in a two-year follow-up. The reduction in tremor may, however, be transient in some patients. Our results suggest that unilateral GKT may have more long-term efficacy in tremor reduction in ET patients than in PD patients. No side effects were observed in our study, leading us to conclude that GKT performed in an experienced centre is a procedure with a good safety profile, despite a lack of intrasurgical monitoring.

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