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Long-Term Patient-Reported Outcome of Radiofrequency Thalamotomy for Tremor

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Keywords
Efficacy · Patient-reported outcome · Safety · Thalamotomy · Tremor

Abstract
Background: Thalamotomy is an endorsed treatment for medication-refractory tremor. It used to be the standard, but nowadays deep brain stimulation (DBS) has become the treatment option of choice. Nevertheless, DBS has the disadvantage of hardware failure, battery replacement, and frequent setting adjustment. Radiofrequency (RF) thalamotomy lacks these issues, is relatively inexpensive, and has a broad applicability in patients with significant comorbidity. Therefore, we analyzed the long-term patient-reported outcome of RF thalamotomy in a cohort of patients with an otherwise intractable tremor. ***Methods:*** A single-center cohort of 27 consecutive patients with intractable tremor was assessed after unilateral RF thalamotomy. Over time, 4 patients had died because of non-related causes. In total, 21 patients responded to a telephone survey to assess their personal judgment on postoperative tremor severity, using a validated tremor scale, adverse events, recurrence, and patient satisfaction. The median time between surgery and telephone survey was 39 months (range 12–126). Seven patients had an additional analysis with postoperative imaging, video-assisted electromyography tremor registration, and a self-reported treatment effect (SRTE) assessment. ***Results:*** Nineteen out of 21 patients (90.5%) reported absence or significant improvement of their tremor. The rating score (WHIGET/UPDRS-III) dropped significantly from a mean of 3.57 preoperatively to 1.05 postoperatively ($p < 0.001$). Eleven patients (52.4%) reported adverse events, but the majority (76.2%) did not consider the adverse events to be severe. SRTE assessment showed a direct postoperative effect of 89.6 of 100 points (SD 10.8), with a gradual decrease to 75.3 (SD 23.5) during follow-up. ***Conclusions:*** RF thalamotomy is a very effective long-term treatment for medication-refractory tremor and should therefore be considered in patients with a refractory unilateral tremor.

Introduction

Tremor is the most common expression of all movement disorders [1]. In the early days, surgery was the only treatment option for tremor. Pyramidotomy, rhizotomy, and chordotomy could reduce tremor, but side effects as weakness and spasticity were common [2]. In 1954,

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Hassler and Reichert [3] described that a lesion in the thalamus could significantly relieve tremor, which made radiofrequency (RF) thalamotomy the preferred surgical treatment since then. In 1987, Benabid et al. [4] introduced thalamic deep brain stimulation (DBS). Schuurman et al. [5] compared thalamic DBS and RF thalamotomy for tremor and concluded that both were equally effective, but that RF thalamotomy had more adverse events and less improvement in function. Since then, thalamic lesioning has been largely ignored, and DBS became the standard care for tremor. However, DBS has disadvantages, including the risk of hardware failure, battery replacements, and multiple hospital visits for adjustment of settings [6, 7]. RF thalamotomy lacks these hardware-related issues, is relatively inexpensive, and has a broader applicability in patients with comorbidity. Therefore, a contemporary reappraisal on RF thalamotomy versus DBS is warranted, based on patient-reported outcome measures (PROMs).

Materials and Methods

A single-center cohort of 27 consecutive patients with intractable tremor was treated with unilateral RF thalamotomy. Over time, 4 patients died due to non-related causes. The remaining 23 patients were requested to participate in a telephone survey to assess PROMs. Two patients were not willing to participate for no apparent reason. An additional prospective analysis was performed in 7 patients to assess self-reported treatment effect (SRTE) using a Visual Analogue Scale (VAS) survey, postoperative 3T-magnetic resonance imaging (MRI), and video-assisted electromyography (EMG) tremor registration.

Patient-Reported Outcome Measures

Telephone PROM survey was done in 21 participants (7 essential tremor [ET], 7 tremor-dominant Parkinson's disease [PD], 4 Holmes tremor, 3 cerebellar tremor) to evaluate tremor severity, recurrence, adverse events, and satisfaction. The Washington Heights-Inwood Genetic Study of Essential Tremor (WHIGET) rating scale was used for all patients with ET, Holmes tremor, and cerebellar tremor. The Unified Parkinson Disease Rating Scale (UPDRS-III) was used to evaluate the effect on tremor in patients with a tremor-dominant PD. Both validated 4-tier tremor rating scales were applied to rate the tremor before and after RF thalamotomy [8, 9]. Following the tremor rating, all participants were interviewed about recurrence, adverse events, and satisfaction. Participants were asked to compare their tremor to the preoperative (absent, improved, unchanged) and directly postoperative (improved, unchanged, worsened, does not know) situation, and to the time between surgery and recurrence of tremor (not applicable, <1, <3, and <6 months, <1, <5, and <10 years). Participants had to answer questions about adverse events (yes or no), the course of these events (not applicable, absent, improved, unchanged, or worsened) and type of adverse events (motor, sensory, speech, psychological, visual). Finally, participants rated their satisfaction after surgery (very satisfied, satisfied, somewhat satisfied, unsatisfied, very unsatisfied, does not know). The median follow-up time was 39 months (range 12–126).

Table 1. Outcomes of the telephone PROM survey

Tremor compared to preoperative	Absent	38.1%
	Improved	52.4%
	Unchanged	9.5%
	Worsened	0.0%
Tremor compared to direct postoperative	Improved	0.0%
	Unchanged	47.6%
	Worsened	47.6%
	Does not know	4.8%
Time between surgery and recurrence of tremor	Not applicable	52.4%
	<1 month	4.8%
	<3 months	9.5%
	<6 months	23.8%
	<1 year	0.0%
	<5 years	4.8%
	<10 years	4.8%
Adverse events after surgery	Yes	52.4%
	No	47.6%
Course of adverse events	Not applicable	47.6%
	Absent	0.0%
	Improved	14.3%
	Unchanged	38.1%
	Worsened	0.0%
Adverse events, *n*	Motor	6
	Sensory	1
	Speech	7
	Psychological	1
	Visual	0
Satisfaction after surgery	Very satisfied	47.6%
	Satisfied	28.6%
	Somewhat satisfied	14.3%
	Unsatisfied	4.8%
	Very unsatisfied	0.0%
	Does not know	4.8%

Additional Analysis

In addition to the telephone PROM survey, 7 of the 21 patients consented to join an additional analysis in the hospital (3 ET, 2 tremor-dominant PD, 1 Holmes tremor, 1 cerebellar tremor). These participants were requested to rate the effect of RF thalamotomy on their tremor on a VAS (0–100 points). A score of 0 points indicated no effect on tremor severity; a score of 100 points meant that tremor was completely abandoned after surgery. MR imaging was performed on a 3T-MRI scanner with a 32-channel head coil (Philips, The Netherlands). Volumetric T2-weighted 3D-Sense was used to determine the location of the thalamic target. Stereotactic software (BrainLab, Germany) was used to define target coordinates. Postoperative video-assisted tremor registration with surface EMG was performed in all seven participants. BrainRT

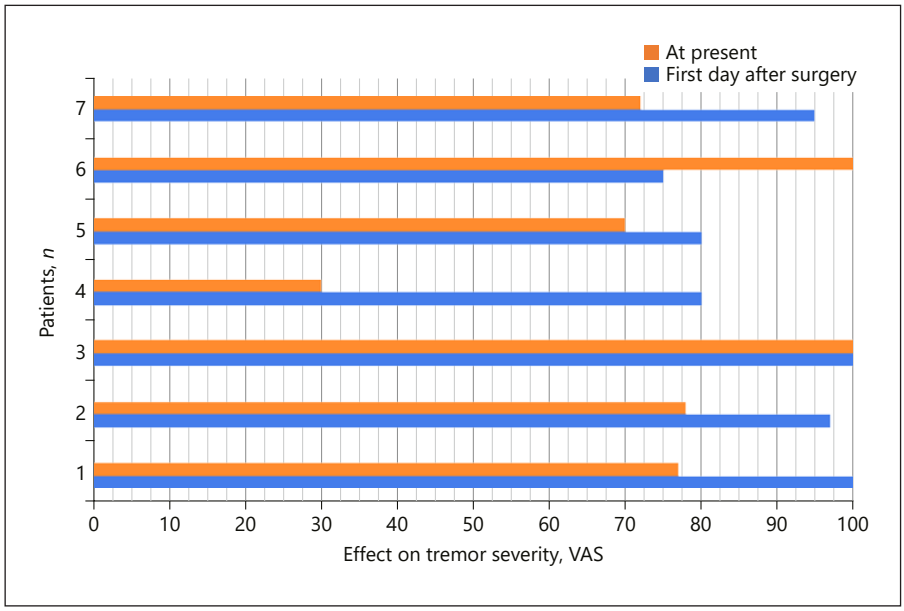

Fig. 1. Patient-reported treatment effect on tremor severity after thalamotomy on a scale from 0 to 100. 0 = no effect on tremor, 100 = tremor is absent.

software (OSG, Belgium) was used to register the tremor following standard protocol. Participants were asked to perform different tasks for at least 30 s in order to measure resting tremor, postural tremor, and intention tremor. The data was analyzed by two independent clinical neurophysiologists. Tremor severity was determined by frequency and amplitude. Clinical tremor degree was rated with the Bain and Findley Clinical Tremor Rating Scale (BFCTRS). This scale includes clinician-based ratings from 0–10 and is recommended by the Movement Disorder Society in the assessment of tremor severity in the head and upper limbs [10]. Postoperative video-assisted tremor registration with surface EMG, 3T-MRI, and the SRTE were assessed on the same day and performed after a median period of 18 months after surgery (range 10–117).

Results

Patient-Reported Outcome Measures

The telephone PROM survey demonstrated that the 4-tier tremor score significantly decreased from a mean of 3.57 (SD 0.60) before surgery to a mean of 1.05 (SD 1.16) after surgery ($p < 0.001$). Overall, 90.5% of the patients reported improvement or absence of tremor after RF thalamotomy. Ten patients reported no recurrence of tremor after surgery. Five of these patients had tremor-dominant PD. In 10 patients, tremor slightly deteriorated during follow-up (from 0 to 1 on the tremor score), mostly within 6 months after surgery (8 patients); the other 2 recurrences happened within a time span of 5–10 years. Fortunately, in all patients with a recurrence still a significant improvement was noted, with a mean tremor score of 1.60 (SD 0.84) ($p < 0.001$). Only 1 patient, with a Holmes tremor due to an ischemic stroke, reported no effect of thalamotomy.

Adverse events were reported by 11 patients (52.4%), temporary in 3 patients (14.3%), mostly motor and speech deficits. Despite this drawback, 76.2% of the patients stated to be very satisfied or satisfied with the result of RF thalamotomy (Table 1).

Additional Analysis

The additional prospective analysis showed the following results. The mean SRTE score on the first day after surgery was 89.6 points (SD 10.8), while the mean score at follow-up was 75.3 points (SD 23.5). A paired-sample t test showed no significant difference between both scores ($p = 0.154$) (Fig. 1).

The T2-weighted MRI commonly showed a demarcated hyperintense lesion at the site of the thalamotomy in most patients (Fig. 2). The mean volume of the lesion was 107.7 mm^3 (SD 56.4), with various shapes. In 1 patient, the lesion was not well defined. Pearson's correlation coefficient ruled out correlation between the lesion volume and SRTE [$r = 0.025$; $p = 0.963$; $n = 6$].

Video-assisted tremor registration with BFCTRS-grading confirmed the findings of the telephone PROM survey. Five patients (71.4%) had no residual tremor after thalamotomy, corresponding to the WHIGET and UPDRS-III in these patients. One patient had mild residual resting and postural tremor; 1 patient had mod-

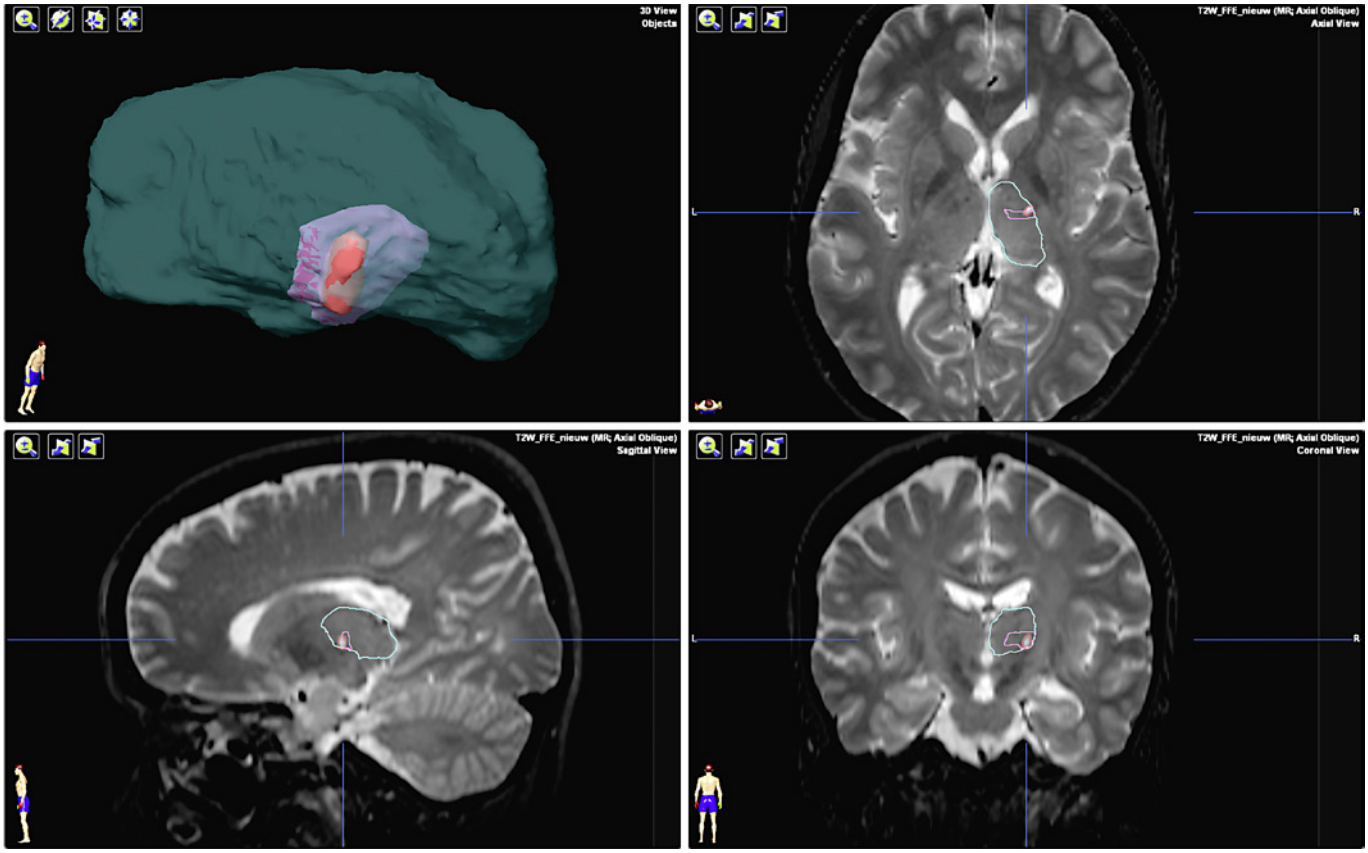

Fig. 2. T2-weighted MRI image of the brain of one of the participants. A well-defined hyperintense lesion is visible in the VIM region of the right hemisphere. The right thalamus (blue) and VIM region (pink) are autosegmentated using BrainLab software. Thalamotomy (red) is drawn by hand.

erate to severe residual tremor. Nevertheless, this patient was very satisfied and had no adverse events. This patient had absence of tremor for 2 days after the surgery, with slow recurrence of tremor in a time span of 4 years.

Discussion

Nowadays, in contrary to the situation in the 20th century, we acknowledge that the opinion and judgment of the patient on treatment outcome is essential for medical professionals to decide on treatment options. Therefore, this PROMs study not only provides insight in the effectiveness and safety of RF thalamotomy for intractable tremor, but also on how this is considered by the involved patient. This study nicely shows that the PROMs after RF thalamotomy significantly improved, with a long-duration effect in the majority of patients. Only 1 other study reported the PROMs after thalamotomy but lacked an additional analysis to verify the results of the non-validated patient telephone survey [11]. Our additional prospective subgroup analysis with SRTE, EMG tremor registration, and BFCTRS supported the results of the telephone PROM survey, which is a nice confirmation of the outcomes measured with the PROMs.

Patient-Reported Outcome Measures

In this single-center study, 21 patients were approached for a telephone PROM survey. All but 2 patients (90.5%) reported the absence or a significant improvement of tremor after RF thalamotomy. On the tremor rating score (WHIGET/UPDRS-III), a significant decrease from a mean of 3.57 before surgery to 1.05 after surgery was noted. This difference clearly demonstrates that RF thalamotomy is very effective. Remarkably, this study

also shows a long-lasting effect on tremor in patients with tremor-dominant PD, despite its progressive nature. Only 1 tremor-dominant PD patient mentioned a very slight recurrence of tremor compared to the first day after surgery within a time span of several years.

Eleven patients (52.4%) reported mainly mild dysarthria and gait disturbance as adverse events. These numbers are comparable to the randomized controlled trial of Schuurman et al. [5]. Similar adverse events were encountered after DBS, but thalamotomy had a higher rate (p = 0.024) [5]. Nevertheless, the overall satisfaction rate in our PROM survey indicates that patients judge the adverse events as mild and justifiable. Notably, none of the patients with adverse events were unsatisfied after RF thalamotomy.

Additional Analysis

In 7 patients, VAS scores were applied as an additional quality-assurance of the PROM survey, since these are validated for patient satisfaction after other interventions as well [12]. As such, it was shown that in this study the SRTE rates of RF thalamotomy were similar to DBS. Børretzen et al. [13] reported a direct postoperative score of 8.5 and a score of 7.4 at follow-up in DBS-patients. These numbers are equivalent to the results in the present study; 8.9 and 7.5, respectively. With MRI, various shapes and volumes of the RF lesion were demonstrated, although the RF thalamotomy protocol was the same in all 7 patients. The smallest lesion had a volume of 51 mm^3, and the largest lesion was 196 mm^3. Nevertheless, Pearson's correlation coefficient did not show a correlation between lesion volume and SRTE. Finally, all 7 patients in the additional analysis underwent an EMG video-assisted tremor registration. This provided an additional objective view on tremor severity, confirming findings of the telephone PROM survey.

Limitations

This study has some limitations. The retrospective nature is the most important drawback, leading to variable outcome measures and variable intervals. In order to verify the results of the telephone PROM survey, we conducted an additional analysis with objective EMG tremor registration and clinical tremor score using the BFCTRS. Furthermore, the small sample size is a limitation of this additional analysis. However, with an important outcome overall, our study supports the long-term efficacy of RF thalamotomy in otherwise non-treatable patients with a severe tremor and a mild adverse event pattern.

Lesioning Techniques

In this study, we demonstrate that RF lesioning is an invasive but effective and patient-satisfying procedure to treat medication-refractory tremor. Nevertheless, there are also non-incisional lesioning techniques available that aim to avoid the surgical risks related to RF thalamotomy; e.g., hemorrhage and infection. Gamma Knife radiosurgery uses ionizing radiation energy to inflict a lesion without the need for a skin incision or a burr hole. However, these lesions evolve over time, and therefore there are no direct clinical effects, nor direct side effects [14]. In this perspective, MR-guided focused ultrasound (MRgFUS) is a promising novel technique. This method is gaining interest because of its immediate effect, controlled administration, and accuracy due to the MR guidance. MRgFUS treatment has been proven effective for the reduction of tremor in ET and tremor-dominant PD compared to the sham procedure [15, 16]. However, studies on long-term effects as well as a direct comparison with RF lesioning are lacking. Since a recent systematic review reported the highest overall rate of persistent side effects after MRgFUS, compared to Gamma Knife radiosurgery and RF [17], in our opinion RF thalamotomy is still the preferred option.

Conclusion

This study demonstrates a very good long-term patient-reported outcome of RF thalamotomy for intractable tremor, comparable to DBS from the patients' standpoint. Furthermore, this study makes clear that patients are willing to withstand permanent adverse events in order to achieve relieve of tremor. Therefore, RF thalamotomy should be reinstated as a valuable tool in the armamentarium of functional neurosurgeons to treat intractable unilateral tremor, to be discussed with the patient as a viable alternative to unilateral DBS.

Acknowledgement

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Statement of Ethics

Research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Subjects (or their parents or guardians) have given their written informed consent, and the study protocol was approved by the institute's committee on human research.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Rik W.J. Pauwels: Acquisition and analysis of the data; drafting the article; critically revising the article.

D.L. Marinus Oterdoom: analysis of the data; critically revising the article.

Gea Drost: analysis of the data; critically revising the article.

Teus van Laar: interpretation of the data; critically revising the article.

J. Marc C. van Dijk: design of the study; interpretation of the data; critically revising the article.

All authors gave their final consent for publication.

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