SIMULTANEOUS RADIOFREQUENCY VIM THALAMOTOMY AND POSTEROVENTRAL PALLIDOTOMY FOR MANAGEMENT OF DYSTONIC TREMORS

Salah M. Hamada, Mohammed Eid, Shafik Tahseen El Molla, Emad H Abouelmaaty, Ahmed Darwish

Neurosurgery Department, Faculty of Medicine, Ain Shams University, Abbasya, Cairo, Egypt.

Corresponding Author:
Salah M. Hamada

Tel: 002-01000231838

E-Mail:
salahhamada@gmail.com
Received: 1/11/ 2022
Accepted: 17/11/ 2022

Online ISSN: 2735-3540

ABSTRACT:

Background: *Dystonic tremors (DT) are complex poorly understood uncommon types of tremors, that are challenging to diagnose and often refractory to medical treatment, Botox injection has been used in selected DT cases and surgical treatment, mainly deep brain stimulations, has been used to treat severe cases, however the role and effectiveness of surgery in treatment DT is still not well established.*

Aim of the work: *To assess the efficacy and safety of surgical treatment of dystonic tremors through simultaneous posteroventral pallidotomy and VIM thalamotomy reporting the surgical procedure, clinical outcome and the complications.*

Patients and methods: *Nine patients with dystonic tremors with different etiologies has been surgically treated with simultaneous pallidotomy and thalamotomy three patients with primary dystonia, two with previous head injury, two with previous cerebrovascular stroke and one patient with postencephalitic secondary dystonia and one with DT secondary to Wilson's disease.*

Results: *All the nine patients improved significantly after surgery with mean improvement of 76%, the highest improvement was in the patients with dystonic tremors with primary dystonia 91 % and the least with post stroke dystonic tremors patients (38%), complications were mild and /or transient this improvement was maintained for all but one patient at 6 months follow up.*

Conclusion: *Simultaneous pallidotomy and thalamotomy can offer an effective surgical treatment modality to treat dystonic tremors of different etiologies with relatively high safety and significant efficacy.*

Key words: *Dystonia, tremors, dystonic tremors, pallidotomy, thalamotomy.*

INTRODUCTION:

The term "dystonic tremors" was first introduced in the literature in the 1980s when dystonic patients were noted to commonly have patterned rhythmic movements, specifically in the upper limbs and the cervical region, demonstrated as tremor.[1] This notion was not easily accommodated, and the current agreement of the Movement Disorder Society characterizes the dystonic tremors (DT) by having three main features: an associated dystonic posture, non-uniform amplitude and variable frequencies and postural or intentional tremors rather than rest tremors. [2]

The Hallmark of dystonic tremor (DT) is the coexistence of tremor and abnormal dystonic posturing in the same body part, which distinguishes it from tremor associated with dystonia, a more generalized form of tremors observed in dystonic patients happening in body segments that are not affected by the dystonia. [3]

The prevalence of DT is still unknown. In a cross-sectional study from Brazil, 22.5% of patients diagnosed with primary dystonia and 21.5% of patients with secondary dystonia had postural hand tremors, [4] In another study from a large movement disorder center in India, dystonic tremor was found in 20% of all patients diagnosed with non-parkinsonian and non-cerebellar tremors. [5]

Similar to other forms of tremors, the efficacy of drug therapy in DT is generally discouraging and only a modest response was found with anticholinergic drugs, clonazepam, primidone, tetrabenazine, β-blockers, while levodopa was only helpful in DT associated with dopa-responsive dystonia.[6] Intramuscular injection with Botulinum toxin, however, provided some improvement, especially for the treatment of axial tremors (vocal cords or neck). [7]

Surgical management of different tremor syndromes and of medically intractable dystonia have been well established.[8] GPi deep brain stimulation provides marked improvement in patients with primary dystonia, Vim is the classic target in patients with essential tremors. In cases of medically intractable DT, DBS provides an important therapeutic option. However, the surgical target of choice in management of DT remains unsettled, previous reports has shown GPi, Vim, and Zona incerta DBS to be significantly effective targets in intractable DT.[9]

We present our experience in surgical management of patients with dystonic tremors through simultaneous radio-frequency posteroventral pallidotomy and vim thalamotomy reporting the surgical procedure, clinical outcome, and safety.

PATIENTS AND METHODS

Of the patients with dystonia undergoing surgery at our institute in the period between 2012 to 2019, nine patients with dystonic tremors were treated surgically, those patients were chosen to undergo simultaneous pallidotomy and thalamotomy contralateral to the side of the dystonic tremor.

The dystonic tremors had different etiologies and were either isolated or as a part of segmental, multifocal, or generalized dystonic syndromes

All patients showed incapacitating dystonic tremors despite receiving pharmacotherapy for at least three years.

The etiology of the DT varied from being a part of primary genetic dystonia in 3 patients, post cerebrovascular stroke in 2 patients, as a sequelae of severe head injury in 2 patients, secondary to Wilson's disease in one patient and as a part of secondary post encephalitic dystonia in one patient.

Preoperative baseline neurological evaluations were conducted, and the patients were evaluated one day postoperatively and came back for evaluation at, three and six months postoperatively.

The patients were assessed using a 5 tier score similar to the UPDRS III tremor sub-score from zero to 4 where zero means no tremor 4 marked tremors present in all or most of the time. Table (1).

Table (1): The tremor score scale used to assess tremors pre and postoperatively

Score	Tremor
0	Absent
1	Slight and infrequently present.
2	Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
3	Moderate in amplitude and present most of the time.
4	Marked in amplitude and present most of the time.

Operative Technique:

Targeting

In the day of surgery the stereotactic frame was mounted to the patient's head (Leksell type G frame; Elekta, Stockholm, Sweden), we took 1.5 Tesla axial T1-weighted images compatible with the planning software through the whole skull and T2 - weighted images proton density

images through the area of the thalamus and the basal ganglia.

We chose the initial pallidal target to be at 2–4 mm anterior to the mid-commissural point (MCP), 4–6 mm inferior to axial plane of the intercommissural line, and 18–22 mm lateral to the midline, to lie in the posteroventral medial portion of the globus pallidus internus (GPi), while the Vim target was taken 1/4 of the anterior commissure-posterior commissure (AC-PC) distance anterior the PC, 13–15 mm lateral to the midline and at the same axial plane as the AC- PC line or one mm above. modifications were made according to the relative dimensions and size of the skull, the diameter of the third ventricle, and the position of the posterior limb of the internal capsule relative to the Globus pallidus.

Electrode placement:

We started in all cases by the Vim thalamotomy, the frame coordinates were set to the Vim target, the burr hole was done 1 cm Infront of the coronal suture and five cm lateral to the midline, so that the angle of the electrode trajectory would be 70°-75° in relation to the axial plane of the AC-PC and 10°-15° lateral to the sagittal plane. A Radiofrequency (RF) generator (Innomed Neuro N50; Munich, Germany) was used to perform the macrostimulation and the lesioning. An RF electrode with an active tip of 2 mm and 1.8 mm in diameter was inserted down to the target with impedance monitoring. Usually, Impedance used to drop close to the target on reaching the grey matter of the thalamus and the basal ganglia.

Macro Stimulation:

We depended on macro stimulation for confirming the optimal target position. We used low-frequency macrostimulation (2 Hz, 2-ms square-wave pulse, 0–5 V) to gain motor thresholds in order to evaluate the proximity to the internal capsule and high-frequency stimulation (50 Hz, 2-ms square-wave pulses, 0–5 V) to evaluate the proximity to the VC thalamic nucleus, and improvement of tremors.

Radiofrequency Lesioning:

After verification of the target position, a temporary lesion was made at 45 ° C for 10s. the patient was assessed for any neurological deficits, if none, a permanent lesion was performed at 70° C for 60 s. two other permanent lesions were made 2 and 4 mm proximal to the permanent lesion with the same parameters, after accomplishment of the Vim thalamotomy, the stereotactic coordinates of the frame were reset to the pallidal target, and the same macro stimulation, and lesioning parameters were achieved except for the high-frequency stimulation which was used to assess the evaluate the closeness to the optic tract.

A CT scan brain was performed within the first day to assess any hemorrhagic complications, Fig (1), and brain MRI was obtained in most patients within a week to assess the location and the volume of the lesion, Fig (2). All patients were discharged a day or two postoperatively.

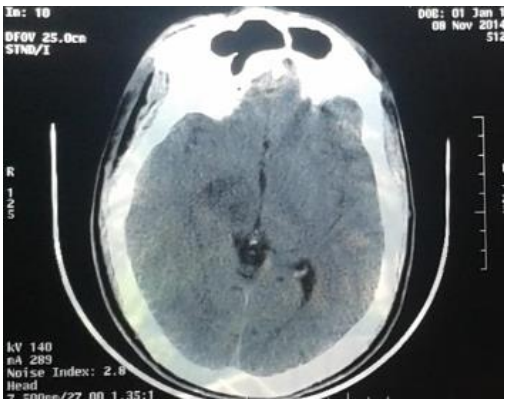

Fig. (1): Postoperative CT scan brain showing the site of the lesion

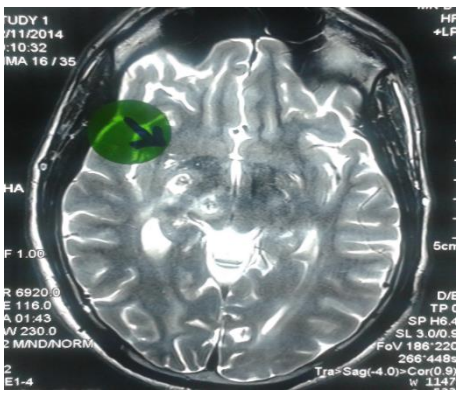

Fig. (2): Postoperative T2 MRI brain of another patient showing the exact location of the two lesions

Statistical analysis:

We used Chi-squared test Fisher's exact test for analyzing the clinical outcome and complications, SPSS software (SPSS, Chicago, IL, USA) was used to perform the statistical procedures, reporting the outcome as statistically significant was done when P-value was less than 0.05.

RESULTS:

Patients' demographics:

Nine patients with dystonic tremors were operated upon in the period between and 2012 and 2019 for simultaneous pallidotomy and thalamotomy contralateral to the side of tremors, four were males and five females, the mean age at the time of surgery was 24.6±9.4, the youngest patient was 16 years old and oldest 41 years old at the time of surgery. Table (2).

Five patients had dystonic tremors as a part of generalized dystonia, three patients had focal dystonic tremors confined to single limb in one of the two post head injury patients and in both post stroke patients, while the patient with Wilson's disease had dystonic tremors in upper and lower limbs on the same side.

Table (2) patient demographics and preoperative and postoperative mean tremor scores

	Patients (n=9)	P-value
Age (mean ±SD)	24.6(±9.4)	
Gender		
Male	4	
Female	5	
Cause of dystonic tremors Primary dystonia Head injury Poststroke Secondary postencephalitic Wilson's disease	 3 2 2 1 1	
Preop. Tremor score (mean)	3.4±0.53	0.012
3m Postoperative tremor score (mean)	0.9±0.8	0.031
6m postoperative tremor score (mean)	1.3±1.1	0.036

Tremor control:

In all our patients, the dystonic tremors improved significantly starting the early postoperative period, this improvement was maintained up to 6 months postoperatively in all but one patient with head injury, this patient had complete resolution of his tremors at 3 months follow-up, however at the 6 months follow-up assessment he had recurrence of his tremors, but he was still better than his preoperative score. The mean tremor score improved by 76% after 3 months from a mean score of 3.4±0.53 to a mean score of 0.9±0.8 (74%) and after 6 months the mean tremors score had a mean of 1.3±1.1 (65% improvement). Table (2)

The maximum improvement was seen in the patients with primary dystonia 91%, while improvement in the tremor score was the least in the patients with dystonic tremors secondary to cerebrovascular stroke (38%)

We had no major complications in our patients, four different complications took place in our patients patients, one patient had homonymous hemianopia, another patient suffered transient weakness contralateral to the lesion side which resolved in one month, a third patient had Transient worsening of speech, deterioration of gait occurred in one patient who had postencephalitic DT, he had deterioration of gait postoperatively which has also

improved to the same preoperative gait in 3 months.

DISCUSSION:

Dystonic tremor is a clinical entity that is still ill defined. four characteristics were defined by the Movement Disorder Society to identify dystonic tremor: dystonic posture in the same body part affected with dystonia, non-uniform amplitude and variable frequency <7 Hz; and postural or intentional tremor rather than rest tremor. [10]

In many patients with task and position specific tremors, the diagnosis of dystonia might be delayed or missed and, as a typical features of dystonia, tremors might not appear until several years after the onset of dystonia [11], also, sometimes it may be challenging to differentiate between ET and dystonia as there is a well-recognized phenomenological overlap.[12] Patients typically have severe functional impairment and mostly shows poor response to the drugs typically used to treat tremor and/or dystonia [6]. All our patients had poor or no response to adequate doses of clonazepam, olanzapine and haloperidol.

Botulinum toxin injection has been reported as an efficient therapeutic option in reducing dystonic tremors especially when focal in distribution, however most of our patients (6/9) had their dystonic tremors a part of generalized dystonia or segmental dystonia warranting more proximal approach for management, the other three patients had focal dystonic tremors confined to a single limb in one head injury patient and both poststroke patients, all the three of them received botulinum toxin injection, the post head injury patient showed no improvement after injection, while the two poststroke patients had transient moderate improvement, and they chose to proceed for stereotactic ablative surgery

Surgical treatment of dystonia has been well established, with proven efficiency of deep brain stimulation and pallidotomy in improving primary dystonia, [13, 14] also thalamic DBS and thalamotomy are being successfully used in the treatment of different types of tremors [15] , however in cases of dystonic tremor syndromes, especially dystonic tremor, the literature lacks a well-established evidence for the effect of surgical treatment weather DBS or lesioning on the dystonic tremor and also the target of choice best used to control these movements

Only few case reports can be found in the literature describing DBS for management of refractory dystonic tremor.[15,16] One report describes the significant improvement of a patient with essential tremor associated with cervical dystonia after bilateral STN DBS. [17] Another report by Morishita et al. described the results of three patients with dystonic tremor who were successfully treated using Vim DBS[18], Ablative therapy, however, weather pallidotomy or thalamotomy has only been very rarely reported in the literature

This is, to our knowledge, the first study to report ablative surgical procedures in treating DT and showing improvement that competes the result of the usage of DBS.

We had surgically treated nine patients with dystonic tremors due to different etiologies, we chose to target both GPi and VIM nuclei because we believed that choosing the VIM alone, which is the thalamic cerebellar receiving area, will be effective in improving the tremors which are not dystonic in origin, and in cases of dystonic tremors a dystonic element in the pathogenesis and phenomenology of tremors exist which should respond better on adding a pallidal target especially in severe cases this was also reported by Peter Hedral and colleagues [9]

DT is common feature of primary dystonia and can be considered as a part and parcel of the clinical phenomenology of the

disease [19] Pallidal DBS and pallidotomy has been proven effective management in primary dystonia [13,14] three of our patients had primary dystonia with severe bothersome dystonic tremors, unilateral in one patients and bilateral asymmetric in the other patients, they couldn't proceed for pallidal deep brain stimulation due to financial reasons and were scheduled for pallidotomy to treat their dystonia with the addition of a VIM thalamotomy contralateral to the tremor side (or contralateral to the most bothersome tremor side in case of bilateral DT), in those three patients the tremors improved significantly with 91% reduction of their preoperative scores. Weather this could be attributed to the pallidal ablation solely needs further research including direct comparison between lesioning (or stimulation) of the GPi alone and combining GPi and VIM.

Different tremor types including dystonic tremors have been reported after ischemic or hemorrhagic cerebrovascular stroke, post-stroke tremors is particularly refractory to pharmacotherapy. [20,21]

In advanced cases, DBS of the thalamic nuclei Vim, Vop, or both, or sometimes the lenticular fasciculus can be therapeutic options. [22] Elias and colleagues reported the effect of deep brain stimulation in a series of 14 patients with focal or unilateral poststroke tremors, four (29%) improved completely and ten (71%) partially.[23]

We had improvement in our both poststroke patient after surgery with 38 % reduction of their tremor score, however this was significantly less than the improvement observed in our other patients with DT weather of primary or secondary etiologies.

The improvement of dystonic tremors in our cases was sustained up to 6 months after surgery except for one patient who had dystonic tremors following severe head injury he was a 24-year-old man who had a high velocity road traffic accident fifteen years prior, this led to severe head injury requiring prolonged intensive care admission with mechanical ventilation and intense rehabilitation, he recovered after four months with no cognitive impairment but there was complex involuntary hyperkinetic movement with predominant dystonic tremors in his left upper limb with failure of right gaze by the left eye. His MRI showed right anterior thalamic small lesion which has been previously reported in cases of DT.[24] He showed no response to pharmacotherapy in the form of clonazepam, olanzapine and haloperidol. postoperatively the patient showed dramatic improvement in the tremors of the whole left upper limb with the ability to use this limb again. In the 3 months follow up the patient still has the same degree of improvement but 6 months after surgery the patient started to suffer again of moderate tremors that was bothersome to the patient but still better than preoperative tremor score

Complications of thalamotomy and complications pallidotomy were reported in large series of patients which apart from hemorrhagic complications are mostly transient and or temporary [25,26] in our cases we didn't find increase in complication rate nor new complications in combining both targets

One patient had homonymous hemiopia which is well reported in cases of pallidotomy especially non-MER guided due to affection of the optic tract.[27]Another patient suffered transient weakness contralateral weakness which resolved in one month which might be due to edema or the lesion extending to the Internal capsule. A third patient had transient worsening of speech and the patient with postencephalitic DT had deterioration of gait which improved to the same gait as preoperative in 3 months

One of the main limitations of the current study bedsides the small number of patients is the difficulty in correlating the extent of the clinical effect of the lesioning to the two

targets and the need to define exactly the benefit that each target provides in controlling the symptoms (which target improves which symptoms profile), this requires more research with direct comparison between the combined targeting and each target alone to bring evidence to the target choice according to the etiology and the phenomenology of the DT.

Conclusion:

The management of dystonic tremors remains an undeniable challenge. This multifaceted hyperkinetic movement disorder is often disabling and resistant to pharmacotherapy, combination of pallidotomy and thalamotomy offers a safe and effective surgical option for treatment of intractable dystonic tremors of different etiologies, further research including direct comparison of different targets needs to be performed in order to set up guidelines for surgical management of medically intractable DT.

Ethical considerations:

Our study protocol was reviewed and approved by the ethical board of the department of neurosurgery Ain shams university. written informed consent was obtained from all involve patients enrolled in our study

Consent for publication

Not applicable

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

Funding

The authors declare that they haven't received any funds related to this research

Authors' contributions

Mohammed Eid, Emad Hamza performed the surgery, analyzed and interpreted the patient data regarding the preoperative clinical and radiological findings and early postoperative follow up. Salah Hamada, Ahmed Darwish, Shafik El-Molla assisted in patient selection and late postoperative follow up , data analysis and was a major contributor in writing the manuscript. All authors read and approved the final manuscript."

Acknowledgements

Not applicable

Authors' information

Not applicable

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بضع نواة المهاد والكتل القاعدية المتزامن باستخدام بالتردد الحراري للسيطرة على ارتعاش التوتر العضلي

صلاح مصطفي حمادة، محمد عيد، شفيق تحسين الملا، عماد أبو المعطي، أحمد درويش

قسم جراحة المخ والأعصاب، كلية الطب، جامعة عين شمس، العباسية، القاهرة، مصر.

مقدمة : ارتعاشات التوتر العضلي هي أنواع معقدة وغير شائعة من الارتعاش والتي يصعب تشخيصها وغالبًا ما تكون مقاومة للعلاج الطبي، وقد تم استخدام حقن البوتكس في بعض الحالات المنتقاة من ارتعاش التوتر العضلي، والعلاج الجراحي وخاصة التحفيز العميق للدماغ، تم استخدامه لعلاج الحالات الشديدة. ولا يزال دور وفعالية الجراحة في علاج هذه الحالات غير مثبت جيدًا

الاهداف : لتقييم فعالية وسلامة العلاج الجراحي للرعشات المتوترة من خلال بضع نواة المهاد والكتل القاعدية المتزامن باستخدام بالتردد الحراري وتقرير النتائج السريرية والمضاعفات الواردة عن الإجراء الجراحي.

المرضى والطرق : تم علاج تسعة مرضى يعانون من رعشات خلل التوتر مع مسببات مختلفة جراحيًا من خلال بضع نواة المهاد والكتل القاعدية المتزامن باستخدام بالتردد الحراري، ثلاثة مرضى كانوا يعانون من خلل التوتر العضلي الأولي، واثنان مصابان سابقًا بإصابات شديدة في الرأس، واثنان مصابان بسكتة دماغية وعائية سابقة ومريض واحد مصاب بخلل التوتر العضلي الثانوي التالي للدماغ ومريض آخر مصاب بخلل التوتر العضلي الثانوي التالي لمرض ويلسون

النتائج :تحسّن جميع المرضى التسعة بشكل ملحوظ بعد الجراحة بمتوسط تحسن 76٪ وكان التحسن الأعلى في المرضى الذين يعانون من رعشات خلل التوتر العضلي الأولي 91٪ والأقل مع الرعاش التالي للسكتة الدماغية كانت 38٪ و كانت المضاعفات خفيفة و / أو مؤقتة، وكان هذا التحسن مستمرا للجميع باستثناء مريض واحد في 6 أشهر من المتابعة

الاستنتاج : يمكن أن يوفر بضع نواة المهاد والكتل القاعدية المتزامن باستخدام بالتردد الحراري طريقة علاج جراحية فعالة لعلاج الهزات العضلية من مسببات مختلفة بأمان عالي نسبيا وبفعالية كبيرة