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Review article

Deep brain stimulation for lesion-related tremors: A systematic review and meta-analysis

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ABSTRACT

Deep brain stimulation (DBS) is an effective treatment for essential tremor or tremor in Parkinson's disease. The effectiveness of DBS in reducing tremors that develop after a structural lesion of the central nervous system (such as Holmes' tremor – HT) has only been addressed in case reports or series.

We conducted a systematic review of all published original reports of DBS in central nervous system lesion-related tremor (excluding demyelinating disorders due to their non-static nature). Where available, we extracted data regarding each patient's demographic, tremor and surgical details. Improvement was calculated as a percentage of change in any objective tremor rating scale.

We identified 35 publications reporting on 82 patients. The ventral intermedius nucleus(VIM) of the thalamus was the preferred target (63.6%) and 18.2% targeted globus pallidus pars interna(GPi). Median improvement was 77.5% and 71.4% for patients with post-stroke and post-traumatic tremor respectively. Seven subjects (13.5%) had less than 50% improvement. Therapeutic effectiveness was not associated with age, tremor duration, age of onset or follow-up time. A large range of stimulation parameters were used with median voltage, pulse width and frequency values higher for GPi (4.80 V, 105 us, 170 Hz) than for thalamic stimulation (3.0 V, 90 us, 140 Hz).

DBS reports for Holmes' and lesional tremors treatment are scarce and highly heterogeneous limiting a proper summary analysis and comparisons. Even facing a probable report bias, a high number of subjects with good long-term tremor control were found. These results should promote the creation of tremor registries before clinical trials.

1. Introduction

Deep brain stimulation (DBS) is currently a standard treatment for medically refractory essential tremor (ET) and its effectiveness in treating Parkinson's disease (PD) tremor [1] is also well known. This has increased the interest in using DBS in uncommon types of tremor [1].

Holmes' tremor (HT) is a rest and intention tremor, which can also present with a postural component. It has a slow frequency (usually less than 4.5 Hz), and is believed to be symptomatic even if in some cases no lesion can be clearly demonstrated [2].

HT develops up to 2 years after central nervous system (CNS) lesions, which can result from tumors, infections, stroke or surgery [2]. The majority of tremors loosely defined as post-traumatic tremors (PTT) also fill the criteria for HT – they present a combination of irregular low frequency resting and intention tremor, which is usually worsened by goal-directed movement [1,3]. Although full HT pathophysiology remains obscure, cerebello-thalamo-cortical and dentato-rubro-olivary lesions have been associated with tremor development [2].

The proper management of HT and other symptomatic tremors is limited by the lack of effectiveness of pharmacological approaches, leading to a growing interest in surgical techniques [1]. However, randomized trials are lacking and most data comes from case reports and small series. We performed this systematic review

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to summarize the information currently available on surgical targets, effectiveness and stimulation parameters used in the treatment of HT and symptomatic tremors. We intend to perform an exploratory analysis of the data collected to identify clinical variables that could be associated with better or worse results.

2. Methods

We conducted a systematic literature review on PUBMED of published original reports of deep brain stimulation in HT, PTT or any type of CNS related lesion tremor. The search was done on 07/12/2016 using the string: (“Tremor"[Mesh] OR tremor) AND (“Deep Brain Stimulation"[Mesh] OR DBS OR “Deep Brain Stimulation”). It retrieved 1321 articles, 35 of which were included in the current review (Fig. 1).

We included case reports and case series that reported the use of DBS in patients with PTT, HT or any tremor developing after any traumatic, surgical, vascular, radiation or infectious insult to the CNS. We excluded all patients with HT or any kind of tremor and simultaneous diagnosis of multiple sclerosis (MS), as we intend to address this issue separately (we believe that the non-static nature of MS could limit our interpretation of results).

For each paper, we extracted data regarding the year of publication and the number of patients reported. For each patient, where possible, data was extracted regarding gender, age, diagnosis, time of lesion, type of tremor, electrode coordinates, stimulation parameters, therapeutic effectiveness, the tools used to assess effectiveness and follow-up time. Data was compiled on a predefined datasheet. Improvement was calculated as a percentage of change in any objective tremor rating scale used by the authors. When this information was not available, but there was information regarding functional improvement, this was used. Analysis was performed using Microsoft Excel 2016 and Matlab R2016b.

3. Results

We identified a total of 35 publications reporting on 82 patients with surgery performed in a total of 88 hemispheres. A summary can be found in Table 1. The majority of surgeries were performed with the use of one electrode per side (88.6%), with the remaining using two electrodes per side. Thalamus, and particularly ventral intermedius nucleus (VIM) was the preferred target (63.6%), but 18.2% of the surgeries included globus pallidus pars interna (GPi) targeting.

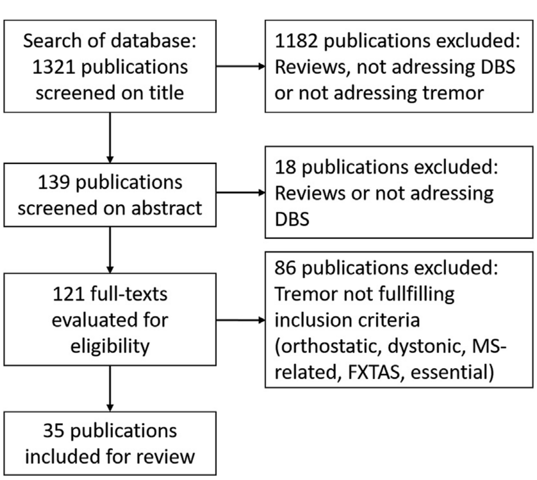

Fig. 1. Flowchart of study selection criteria. DBS – deep brain stimulation. MS – multiple sclerosis. FXTAS – fragile X-associated tremor ataxia syndrome.

In 65 subjects (79.3%) there was information regarding the scale used to assess the tremor (the Fahn Tolosa Marin scale was used in 31, a 5-point rating scale in 17, the Bain tremor rating scale in 9, the tremor scores of the Unified Parkinson's Diseases Rating Scale in 3, Essential tremor rating scale in 3, Washington Heights Inwood Genetic Study of Essential Tremor Rating Scale in 2). However data regarding individual assessment was available for only 52 subjects (a Japanese series of 12 subjects, using VIM/VOA stimulation reported a pooled improvement of 78% [4]).

Although median reported improvement is 75% (IQR: 55.25–88.25%), seven subjects (13.5%) had less than 50% improvement after surgery (Fig. 2). Considering the full dataset, therapeutic effectiveness was not found to be associated with age, duration of tremor, age of tremor onset or to change with follow-up time (Fig. 3).

We then performed separated analyses considering the cause of the tremor. We divided the cohort into 3 groups based on the cause of tremor – those that developed tremor after stroke, after trauma or in relation to any other CNS lesion (Table 1). Prognosis seems to be better for subjects with tremor after stroke (only 1/21 subjects showed an improvement of less than 50% and the median improvement was 80% for thalamic and 77.5% for GPi targets, Fig. 2) when compared with subjects with tremor after CNS trauma (6/23 subjects showed an improvement of less than 50% and the median improvement was 66.7% for thalamic and 54.4% for GPi targets, Fig. 2).

When compared with patients with PTT, those with post-stroke tremor (PST) were, on average older at the time of surgery (43.0 vs. 24.0 years old for thalamus; 43.0 vs. 29.0 for GPi, Supplementary Fig. 1), and also had a shorter duration of disease (1.5 vs. 10 years for thalamus and 7 vs. 9 for GPi, Supplementary Fig. 2). Mean follow-up times were relatively similar between the PST and PTTgroups (1.7 vs. 2.1 for thalamus; 3.2 vs. 2.0 for GPi, Supplementary Fig. 3). No associations were found inside each group with age, duration of tremor, age of tremor onset or follow-up times (Supplementary Fig. 4–7).

We were only able to find reports on effectiveness in treating the different tremor components (rest/action/kinetic) in 19 patients. Similarly, information regarding planned electrode coordinates or final position was only found in 27 out of the 88 hemispheres (30.8%). This limited any detailed analysis relating to targeting and symptom-specific effectiveness.

The stimulation parameters used in the last assessment are summarized in Fig. 4. Although a large range of parameters were used, median voltage, pulse width and frequency values were higher for GPi (4.65 V, 120 us, 160 Hz) than for thalamic stimulation (3.0 V, 90 us, 135 Hz). No clear association was found between the parameters used and therapy effectiveness (Fig. 5), or relevant differences according to the cause of lesion (Supplementary Fig. 8–10).

4. Discussion

Reports on DBS for treatment of PTT or post-lesion tremor are scarce and highly heterogeneous regarding effectiveness report, tremor assessment, target selection and stimulation parameters. Additionally, information was lacking in the target details and tremor semiology. Nevertheless, our analysis summarizes the use of DBS for treatment of HT and post-lesional tremors over the last 15 years. Also, no clear association was found with improvement with age or disease duration (there are reports of cases referred to surgery at 13 and 80 years-old with relatively good results).

Since data was summarized from case reports and small case series we cannot formally estimate the presence or severity of publication bias. However, it is highly likely that reporting of cases

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