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Efficacy & Safety of Deep Brain Stimulation on Tremor in Multiple Sclerosis Patients

Literature Review

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ABSTRACT

Background

Tremor is a complication frequently associated with multiple sclerosis and can be severely disabling in up to 15% of these patients. Deep brain stimulation has been proven effective in other tremulous conditions though it's efficacy and safety in multiple sclerosis patients is not well documented

Methods

Identification of relevant studies published via established databases like MEDLINE, EMBASE and Google Scholar. A quantitative and qualitative review was done on all studies obtained that met the inclusion and exclusion criteria specified.

Results

Tremor suppression achieved at late follow-up across the studies was 85.2% and of those 69.1% documented to have sustained tremor suppression over a one year period. 75% were reported to have gained functional benefit and only 65.5% documented to have sustained improvement over a one year period. Associated adverse effects more prevalently documented were infection at site of implantation, intracerebral haematoma, exacerbation of MS, dysarthria and peri-operative seizures

Conclusion

Deep brain stimulation is effective in the symptomatic relief of tremor in multiple sclerosis patients. The benefits gained depend on long-term stimulation and require patients to be compliant with regular follow-up. The subthalamic region has proved to be a more efficacious target as compared to the traditional ventral intermedius nucleus. Despite the good outcome, this procedure is associated with risk and has to be weighed against potential benefits.

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Introduction

Multiple sclerosis (MS) is one of the most common central demyelinating disease globally especially in Northern European and American regions. Tremor is a frequent complication of MS seen to be affecting 25% to 58%[1] of MS patients. It is associated with involvement of the upper extremities (55%), lower extremities (8%), head (7%) and trunk (5%)[3]. **Matsumoto et al[4] defines MS tremor as intermittent or continuous, involuntary movements of the upper extremity that appeared rhythmic and oscillatory to visual inspection in a patient with clinically definite MS.** Anatomy of the basal ganglia and the specific thalamic nucleis is very important to understand when considering the pathophysiology of MS tremor and deep brain stimulation (DBS) (fig 1).

The tremor is postulated to be caused by synchronisation of discharging motor units due to complex interactions between neuroanatomical structures with the MS related pathological peripheral reflexes and central oscillators[5]. It is also hypothesised that there is a direct effect based on location of these lesions manifesting in MS tremor. Tremor in MS is thought to be caused by lesions at the cerebellar level and it's associated tracts[1], thus manifesting in tremor that is based on the lesions neuroanatomical location. A study in the past though, showed a correlation between lesion burden in the pons, rather than the cerebellum with tremor amplitude[6]. These lesions can lead to other clinical manifestations such as ataxic features of dysmetria, dysarthria or eye movement disturbances. The tremor usually has a proximal and distal component with a large amplitude (2.5-7Hz) postural and kinetic component[7] to it, though concurrent ataxic involvement can make tremor evaluation very difficult[8]. Proximal involvement of the upper extremities can cause large displacements of limbs while the kinetic tremors are enhanced by visually guided goal-directed movements. Thus, tremor in MS can be very severe and tend to dramatically affect quality of life and lead to disability with an approximate of 3% to 15%[1] of MS patients with tremor succumbing to such severity.

Medical treatment aimed at tremor in multiple sclerosis is less than satisfactory and on most occasions are medication resistant[1]. The progressive nature of the disease generally makes the pharmacological options of little functional benefit[2]. Thalamotomy on the other hand is an ablative surgical procedure which has yielded results in certain patients though may not produce long term benefits in some[3,4]. The procedure has been documented to relieve contralateral limb tremor in 65-96% of MS patients though tremor relapse was noted in approximately 20% of patients within 12 months[7]. Thalamotomy has been associated with side effects such as dysarthria, swallowing difficulties and balance disorders which ranges from 0 to 45% in different case series [7]. Due to the drug resistant nature of MS tremor and complications associated with thalamotomy, DBS is a form of treatment which has resulted in good success rates for tremor associated with Parkinson's disease (PD) and essential tremor (ET), is now being used in some cases for treatment of tremor in multiple sclerosis. DBS is thought to cause less side effects than thalamotomy and is reversible compared to the permanent lesioning function of it's counterpart. This new intervention in MS patients is thought to have a dual effect via stimulation of the targeted nucleus within the thalamic or subthalamic region and produces a 'microthalamotomy' like effect which persists for a variable duration. The target of stimulation which is commonly used to produce relief of tremor is the ventral intermedius (VIM) nucleus though there have been various studies proving other targets to produce better alleviation[1,7]. Although this modality of treatment seems promising, the data behind the effectiveness of it has been inconsistent and variable[7]. This paper is a review of the efficacy and safety of DBS on MS related tremor by analysing published reports related to this subject.

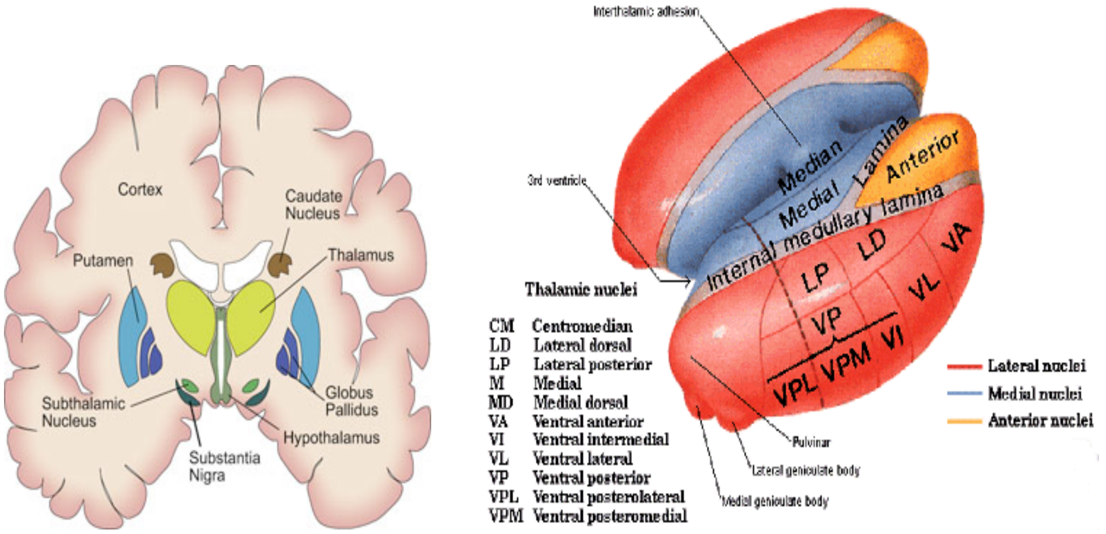

Figure 1- Anatomy of the basal ganglia and the specific thalamic nucleis

Methods

Case reports and clinical studies were obtained using relevant keywords and search terms (deep brain stimulation, multiple sclerosis, tremor, thalamic stimulation) in Medline (1966 to March 2011), EMBASE (1988 to March 2011) and Google scholar. Additionally, the reference list of each study obtained and existing published reviews was then browsed through to extract papers relevant to the subject matter. Papers obtained were than filtered via certain inclusion and exclusion criteria. Studies were included if it encompassed patients with a diagnosis of MS, tremor of any degree, underwent procedure of deep brain stimulation, as well as documented pre-operative and post-operative follow up on tremor. Studies that were excluded were those that did not meet the inclusion criteria, had insufficient data documentation or those studies that were duplicates. Studies of mixed patients populations with other tremor causing conditions such as PD and ET were included if separate data for MS patients outcome were available from the results.

Results

Description of Studies

Among the 28 studies identified there were a total of 151 patients that were suitable for this review. There was variability in patient population sizes ranging from 1 to 15 patients. Studies encompassed largely patients purely with MS treated with DBS though some studies included patients with mixed movement disorder aetiologies or were comparative studies to thalamotomy. Most studies did not specify detailed inclusion and exclusion criterias. Among the more commonly used criteria were severe upper extremity tremor, tremor of an action, postural or intention component, medication refractory tremor, clinically stable MS for at least the past six months and a measure of poor functional capacity (Expanded Disability Status Scale (EDSS) mean of >7). Studies were excluded commonly if patients had sensory loss, muscle weakness, cognitive dysfunction (Mini Mental State Examination (MMSE)<24), ataxia or cerebellar hypermetria, contraindications to surgery or a previous thalamotomy.

Various outcome measures were used across the studies though there was no consistency in terms of assessment scales used. Tremor scoring was carried out with different rating scales that were either designed by the author or a previously established one such as the Fahn-Tolosa-Martin(FTM) rating scale, Tremor-Clinical Rating Scale(TCRS), or the Bain-Finchley tremor scale. Benefit gained by patients were analysed via assessment guides of functional capacity such as Activities of Daily Living(ADL) Index, EDSS, related questionnaires or general patient feedback on surgery and outcomes. Other secondary outcome measures were included in the studies are neuropsychological assessment and post-surgical MRI scans.

Follow-ups periods were variable across all studies and ranged from a period of 2 months to a mean period of 5.2 years in some studies. In majority of studies initial tremor reduction was 100% that were attributed to a "microthalamotomy" like effect. Thus in some studies follow-ups were done at a "safe" period when this effect was postulated to have relieved. In another instance, a regression line was drawn at one month as to negate the "microthalamotomy" effect on the outcome[9].

Surgical Procedure

The VIM has been the selected surgical target for DBS implantation in most of the studies (16 studies) reviewed. The fundamental concept behind DBS is illustrated in fig 2. Some series documented stimulation of other targets like the Ventrocaudal nucleus(Vc) as an indirect effect on VIM stimulation[10]. Other common thalamic targets are the Ventral oralis anterior(VOA), Ventral oralis posterior(VOP) and the ventrolateral thalamus(VL). Subthalamic region especially the Zona Incerta(ZI) has become an increasingly used locus of stimulation in DBS for MS tremor as were seen in 7 studies. Some series documented various targets curtailed for specific tremors and different proximities of limb tremor[11,12,13]. Majority of studies had reported specifics of intraoperative procedures and on techniques used for neurophysiological location of the optimal point of tremor suppression in the selected target. Some studies specified the use of macroelectrodes, microelectrodes or semi-microelectrodes. The usage of both microelectrode for mapping, and macroelectrode for confirmatory purposes and avoiding stimulatory side effects in certain cases were reported[7,14].

Neurophysiological location of intra-operative tremor suppression was detailed via different avenues such as somatosensory mapping, identification of tremor cells, use of Field Potentials(FP), accelerometry or Electromyography(EMG) reading, or achieving a “microthalamotomy” effect . Few studies gave details on final parameters of electrode implantation as well as optimal stimulation settings in pre-operative and post-operative setting. Majority of studies conducted unilateral implantations for contralateral tremor control though some studies had stimulation performed bilaterally, either simultaneously or staged. Implantation was not undertaken in certain patients due to the inability to map optimal point of tremor suppression intra-operatively[15], a benefit from microelectrode insertion alone relieving tremor[15,16] or side effects like the development of an intracerebral haematoma[9], intra-operative seizure[17] or unmanageable wound infection[18]. Some studies used CT, MRI or X-ray to determine final stereotactic coordinates of electrodes that were inserted.

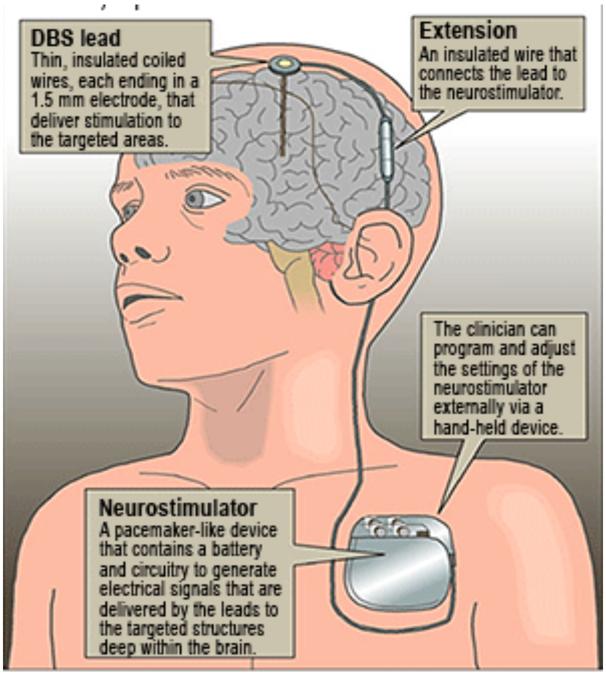

Figure 2: Illustrative overview of Deep Brain Stimulation

Outcome on Tremor And Daily Benefit

Table 1 summarizes the core details from each of the 28 studies. A degree of tremor suppression and improvement in quality of life was achieved in most of the studies. Studies that had clear documentation of percentage of patients whom obtained an extent of tremor suppression were 23, and of those there were 98 patients from a possible 115(85.2%). Among the 8 studies that had mean follow-up periods of more than 1 year, patients that acquired tremor suppression were 38 from a total of 55(69.1%). Functional benefit on daily living obtained via DBS was reported only in 60 patients out of a population of 80(75%). While of those, 19 patients from 29(65.5%) were reported to have maintained functional benefit at follow up mean period of more than a year.

Table 1: Studies of DBS in MS patients and the respective outcomes

Study	Study size (n)	Mean Age(years) / Sex (Male:Female)	Mean MS duration (years)	DBS Specifics	Tremor Suppression[s]	Functional Benefit[s]	Follow-up[μ]
Brice and McLellan 1980[19]	2	23-34 / 0:2	n/r*	Unilateral Subthalamic	100%	100%	5-6 months
Nguyen and Degos 1993[11]	1	35 / 0:1	n/r	Unilateral VIM	100%	100%	17 months
Benabid et al 1996[20]	4	n/r	n/r	VIM	Inconsistent, less significant or not improved**	50%	3 and ≥6 months
Geny et al 1996[21]	13	37 / 5:8	9	VIM Unilateral	69.2%	92.4%	13.4 months mean
Whittle et al 1998[16]	5	n/r	n/r	VLl thalamus	n/r	n/r	n/r
Montgomery et al 1999[9]	14	42.3 / 8:6	12.4	Unilateral VIM	100%	n/a	<3 months to >12 months
Hay 1999[5]	1	37 / 1:0	9	Unilateral thalamic	100%	n/a	2 months
Taha et al 1999[22]	2	n/a	n/a	Bilateral VIM	100%	n/a	10 months
Schuurman et al 2000[23]	5	36.6	n/a	VIM	≥40%^	2.9% increase in FAI[π]	6 months
Matusmoto et al 2001[4]	3	No separate data for DBS	n/a	Unilateral VIM	100%	0%	12 months
Berk et al 2002[18]	12	34.5 / 5:7	n/a	Unilateral VIM	Significant mean reduction by 40%	100%	12 months
Hooper et al 2002[16]	10	41 / n/r	13.3	Unilateral Thalamus	100%	68% or 78% benefited or remained the same based on functional scales	12 months
Nandi et al 2002[24]	1	35 / 0:1	4.5	Unilateral ZI	100%	100%	12 months
Schulder et al 2003[25]	9	43.4 / 0:9	7.4	Unilateral VIM	89%	33%	32months mean
Loher et al 2003[26]	2	71.4#	n/a	Unilateral VIM	100%	100%	9 months
Wishart et al 2003[17]	4	46.5/ 3:1	9	Unilateral VL thalamus	100%	n/a	22 months
Moringlane et al 2004[27]	1	34 / 0:1	14	Unilateral VL thalamus	100%	100%	4 years

Table 1: Continued

Study	Study size(n)	Mean Age(years)/ Sex (Male:Female)	Mean MS duration (years)	DBS Specifics	Tremor Suppression[S]	Functional Benefit[S]	Follow-up[µ]
Nandi et al 2004[12]	15	39.4 / 8:7	10.4	Unilateral VOP and ZI	Mean reduction postural (63.7%), intention (36%)[α]	n/r	15 months
Lim et al 2007[28]	1	42 / 0:1	9	Bilateral VIM and VOA[┤]	100%	100%	9 months
Hyam et al 2007[29]	6	34.2 / 4:2	3.7	Mixed regions	83%	50%	3.67 years
Hammel et al 2007[14]	2	No separate report for MS	n/a	Bilateral Ventrolateral or Subthalamic	100%	No separate report for MS	3 months to ≥1 year
Herzog et al 2007[30]	11	41.5 / 6:5	10.1	VIM	100%	n/r	11.4 months
Plaha et al 2008[13]	4	40.3 / 1:3	5	Bilateral ZI	100%	≥50% [β]	1 year
Moore et al 2009[10]	1	47 / 0:1	7	Unilateral VIM	100%	100%	n/r
Thevathasan et al 2010[33]	11	38.7 / 3:8	12.2	VOP and ZI	63%	54.5%[Ɨ]	5.2 years
Torres et al 2010[7]	10	38.1 / 4:6	15.1	VIM	36.4%	n/r	31 months
Mandat et al 2010[32]	5	37 / 2:3	6	Indirect VIM	100%	100%	3 months
Johnson et al 2010[33]	1	33 / 0:1	11	Unilateral Thalamic	100%	n/r	4 years

S tremor suppression and functional benefit measured as percentage of patients gaining any extent of benefit from DBS

µ follow-up recorded as mean unless a range is given

*not reported

**reported with another 13 patients with other dyskinetic forms of tremor

^ other 60% had tremor relapse though tremor scores were still better or same as pre-operative scores

[П] Frenchay Activity Index

Data mixed with other tremor aetiologies

α Only 10 from 15 patients tremor outcome documented

┤ Assessment also done with VIM and VoA separately which both produced similar results to simultaneous stimulation

β Only two patients were reported to of not being wheelchair bound any longer after DBS, while other two patients did not have functional benefits documented

Ɨ Data at early(<1 year) post-operative no data reported for late follow up

Adverse Effects

Among the 28 studies reviewed, there were 4 cases of intracerebral haematoma where in two cases the patient developed a microhaematoma (use of microelectrode[9] and semi-microelectrode[20] respectively) and other two cases developed small thalamocapsular haematoma[16] (use of macroelectrode). The 2 patients with the thalamocapsular haematoma were left with hemiparetic deficits at one year. One of the patients (not implanted) with the microhaematoma acquired it during surgery and was left with a temporary dysarthria[9]. Though it was postulated that for these 3 patients, the intracerebral bleed gave them better function of their hand via reduction of tremor severity. The remaining 1 patient's microhaematoma resulted in an acute deficit which waned off in 3 months[20].

Dysarthria was evident persistently in 4 cases where it ranged from mild to severe with one documented case of worsening of an existing dysarthria[19]. There were also 4 cases of transient dysarthria which all alleviated within a range of 3 months. Infection at the site of implantation was recorded in 6 patients with an overall incidence of 3.85%. Among those, there was documentation of attempted antibiotic treatment in all patients of which 4[12,16,18] (67%) being successful, though in one patient failure was attributed to cognitive state and behaviour of patient. A single case of memory deterioration was recorded in all studies.

Exacerbation of MS was reported in 4 studies among 8 patients of which 5[9,17,25] occurred within a month of DBS surgery. 3 of those patients was reported to respond to intravenous steroids. The occurance of seizures was 5.6% across all studies. Some studies, reported patients complaining of paresthesia at initial stimulation which settled in about 1 minute though adjusting stimulation parameters provided relief as well. Other transient side effects that was associated with DBS in a minority of patients were hemiparesis, monoparesis, diplopia, swallowing difficulties and abnormal bladder control. Some patients were left with chronic sequelaes like hemiparesis, ataxic features and asthenia.

Neuropsychological studies were done in a small number of series mostly yielding unremarkable results, though Benabid et al[20] postulated that stimulation of the left VIM affected verbal fluency while the right side affected spatial performance. Loher and associates[26] reported reduced short memory recall (episodic memory) on stimulation of it's left side.

Table 2: Adverse effects recorded among studies with DBS in MS patients

Adverse Effects	Number of Cases (n)	Mean Incidence (range)*	Overall Incidence
Transient Dysphagia	1[19]	20%	0.64%
Dysarthria			
Transient	4[9,17,19,29]	17.1%(6.7%-25%)	2.56%
Permanent	4[12,23,19,27]	15.6%(6.7%-20%); 100%[27]**	2.56%
Urinary Complications	5[18,19]	33.4%(6.7%-60%)	3.21%
Transient Monoparesis	4[16,17,21]	17.6%(7.7%-25%)	2.56%
Transient Acute Deficit	1[20]	25%	0.64%
Hemiparesis			
Transient	2[12,29]	11.7%(6.7%-16.7%)	1.28%
Permanent	2[16]	20%	1.28%
Transient diplopia	1[17]	25%	0.64%
Transient Initial Stimulatory Effects			
Dyesthesia	13[21]	100%	8.33%
Paresthesia	Cannot ascertain	Most[9]; Most common[18]; Some[16]; (n=1)25%[17]	Cannot acertain
Arm ataxia	1[23]	20%	0.64%
Ataxic gait	2[23]	40%	1.28%
Impaired mobility	1[13]	25%	1.28%
Intracerebral haematoma	4[9,16,20]	17.2%(6.7%-25%)	2.56%
Wound Site Infection	6[7,12,16,18]	12.2%(10%-15.4%)	3.85%
Wound Inflammation or Erosion	2[17,31]	16.7%(8.3%-25%)	1.28%
Intra-operative Hypoxia	1[16]	10%	0.56%
Memory deterioration	1[25]	25%	0.56%
Seizure	10[7,12,16,17,31,33]	18%(6.7%-30%)	5.6%
Exacerbation of MS	8[9,17,21,25]	22.1%(7.1%-33.3%)	5.13%

*Incidence recorded only among studies with the specific reported side effect

** Only one patient in this study, thus data not incorporated into mean incidence(range) as may skew values, but included in the overall incidence

Discussion

Evidence suggests that DBS provides relief of tremor in patients with MS enhancing further the notion of DBS as an effective form of stereotactic surgery for these patients. Based on the data, DBS also has a proven effect in increasing patient's functional capacity to facilitate better quality of life. Despite the evidence compiled, some pitfalls throughout the studies reviewed have translated onto the quality of data retrieved. Documentation of outcomes especially of functional benefit gained, have not been practiced in many of the studies in which 47% of patients failed to be reported on that aspect. Inclusion criteria's and exclusion criteria should encompass inclusion of patients with clinically stable MS for at least 6 months, drug refractory disease, severe upper extremity tremor with no signs of sensory loss or weakness in the tremulous limb and free of ataxic features. A criteria of clinically stable MS aids in ensuring that the disability status of a patient is assessed purely in terms of DBS efficacy and is not affected by progression of disease. Muscle weakness may have a "false positive" effect on tremor suppression post-DBS. Hyam et al[29] identified a significance between pyramidal weakness and attenuation of intention tremor hence the need for the utilisation of an established muscle strength assessment like the Medical Research Council(MRC) Scale as a filter for only suitable patients to partake in these studies. An underlying ataxic complex needs to be excluded as tremor alleviation can unmask an underlying cerebellar syndrome[8,25] making assessment of tremor difficult and at the same time severely affecting disability scoring.

Success of DBS would stem from not only from improving tremor control but returning a beneficial amount of patient's functional capacity as well. Outcome measures used differed among studies preventing standardised assessment of patients and efficacy of DBS. Scales used such as EDSS must be used with caution especially in patients with MS, while the tremor scales allowed for examiner biasness and does not assess the functionality aspect. Matsumoto et al[4] describes the use of Quantitative Movement Analysis(QMA) to eradicate these two limitations of orthodox tremor scales. In the same study, the author suggested a multi-dimensional battery of test to quantify outcomes accurately. Herzog and associates[30] carried out neurophysiological assessment of postural tremor using electrophysiological measures via accelerometry and of intention tremor using kinematic analysis on top of a conventional lateralised TCRS. This allowed assessment of tremor in terms of spatial variability and allowed for assessment of cerebellar features of MS on tremor control through kinematic analysis. These measures allow for evaluation of functional gain as well through tremor analysis. Validated health-related questionnaires is usually best suited to assess overall functional benefit.

The effectiveness of DBS has been debatable in terms of longevity of benefits reaped by patients. DBS is good value for in the first year of treatment though long term effects have not been as encouraging. Torres et al[7] documents a 50% tremor suppression at one year to a 20% suppression at 3 years among it's patient population and a separate 20% suffered from tremor relapses at less than 2 years. Wishart et al[17] reported 4 patients whom acquired tremor suppression initially, though 3 patients had effectiveness declined over time but still remained at beneficial levels. Hyam et al[29] reported initial tremor reduction in 83% of patient population, to 33% at 2 years or more. These all show marked decline with cases of relapse. Despite that, Thevathasan and associates[31] have showed evidence that long term effective stimulation can provide staggering improvement in mean tremor score of 61.7%, even with a mean late follow up period of 5.2 years. In the same study 80% of patients assessed with stimulation OFF showed no improvement of tremor score in the first year of follow-up, however 60% of the same group went on to achieve tremor reduction in OFF at the late follow-up. Another instance, would be the report of single patients in two studies[27,33] of whom both achieved sustained tremor control for four years, even though in one of the cases it was found that the battery generator had run out.

This points that DBS has long term efficacy with proper compliance, though the stimulatory effects of DBS seems to have a major role in the initial stages of treatment but in the long run a 'persistent microthalamotomy' like effect takes place producing mirrored tremor relief in OFF and ON parameters. In a post-explantation MRI study of 2 patients, lesions were found along the course of electrode tracts in the patient that developed permanent tremor reduction and not in the other. Schulder et al[25] conducted MRI scans that were unremarkable in his studies, though the only histopathological study of post-DBS in MS patients done by Moore et al[10] indicated demyelination of grey matter spreading out from the stimulation site which is vaguely visible on MRI. This goes hand in hand with the theory of stimulation induced demyelination producing the postulated "persistent microthalamotomy" effect. This raises cost-effective questions of the redundancy of battery generator replacements in cases where there is development of this phenomenon. In majority of the cases, reprogramming to optimal parameters were required especially in the first few weeks post-operatively due to the effect of "tolerance".

Brodkey et al.[34] have reported 5 times more Tremor Related Activity(TRA) cells per unit thalamus in PD as compared to MS being one of the reasons for the obvious difference in effectiveness of DBS in tremor of PD as compared to in MS. VIM stimulation has proven results previously and the documentation of it's somatotopic organisation allowed precise stereotactic parameters for an end effect on a specific region[12]. There have been studies done comparing the efficacy of other thalamic targets like the VOA with VIM which showed similar results[28]. Evidence of DBS effects on VIM were shown through the study of motor evoked potentials(MEP) via the cerebello-thalamic-cortical (CTC) pathways with VIM stimulation, and it's effect in restoring motor inhibition within the CTC[35]. In recent times, the subthalamic region has reported to be largely more effective than thalamic targets. Hamel et al[14] and Herzog et al[30] have documented the effectiveness of the subthalamic region in DBS as compared to thalamic stimulation in tremors of postural and intention components. The subthalamic region is thought to be most effective due to it's afferents, the CTC that are projected to the VIM via a narrowed region, hence only requiring a smaller stimulatory field. Subthalamic stimulation though has been reported with higher risk of side effects of dysarthria, paresthesia and gait ataxia accentuated especially with bilateral stimulation when compared to VL thalamus targeting[14].

DBS has proven to be effective and has trumped thalamotomy as it was said to have a smaller risk profile. In a comparative review done by Yap et al[3], initial tremor suppression recorded in both were approximately similar though functional improvement in DBS dwarfed that of thalamotomy, though the risk of haemorrhage in DBS seemed to be higher, 3.09% to 0.62%. This review though estimated a haemorrhagic complication rate of 2.56% for DBS which is still substantially high. Despite this, the irreversibility, the ability to have complete control over degree of tremor suppression and it's longer lasting benefits make DBS more attractive as a treatment option. Though recently, Johnson and associates[33] reported an 8 fold increase in the incidence of seizures in MS patients whom completed DBS compared to other disease groups. From the literature gathered there seems to be an increased risk among the group whom have undergone thalamic procedures rather than subthalamic ones. The seizures seem to be a one off incident with good response to a loading dose of phenytoin. This begs the question whether could this be due to the fact of the prevalence of epilepsy in MS patients (2.3%) with it's natural demyelinating progression, or from an initial stimulatory effect from the DBS device. The overall cost of DBS is estimated to be very high and the average visit per patient for reprogramming was approximated to be 5[36]. Combined with the phenomenon of "tolerance" it is clear that patients need to be committed to treatment highlighting the shortcomings of DBS.

Conclusion

This review has highlighted the efficacy and safety of DBS in the treatment of MS related tremor. It is documented to provide tremor suppression in 85.2% and functional benefit in 69.1% of these patients. Despite that, the long-term outcome depends on the chronicity of implantation as well as patient compliance. Neurophysiological assessment modalities have introduced improved simultaneous evaluation of the multivariable components of MS tremor and functional capacity of the tremulous limb. The subthalamic region should be given consideration as an alternative target to the VIM nucleus in this subgroup of patients. Despite the obvious benefits of DBS, the associated risk of intracerebral haemorrhage(2.56%) and wound infection(3.85%) remains considerable and needs careful exploration to ascertain the safety of this surgical procedure. Of recent, the recognition of MS exacerbation(5.6%) and seizures(5.13%) associated with DBS has highlighted the need to further evaluate these complications to better understand the risk profile of DBS.

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