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A Prospective, Randomized, Blinded Assessment of Multitarget Thalamic and Pallidal Deep Brain Stimulation in a case of Hemidystonia

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Abstract

Objective
Dystonia is increasingly being interpreted as a multi-nodal “network” disorder. We aimed to investigate multitarget DBS (pallidal and thalamic) versus each target alone in a prospective, randomized, blinded trial in a case of hemidystonia secondary to putaminal stroke.

Methods
DBS leads were implanted in the GPi and Vim/Vop and each stimulation combination (GPi, Vim/Vop, and both) was tested for three months in a single patient. Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) and Short-Form 36 (SF-36) were completed at the end of each trial period.

Results
Multitarget (GPi + Vim/Vop) stimulation was clinically the most effective treatment and resulted in the most improvement in function and quality of life. The patient’s hemidystonia improved by 25% as measured by the BFMDRS during the multitarget stimulation trial period and at the 6-month follow-up. The patient’s quality of life improved by 86% and 59% during the multitarget stimulation trial period and at the 6 month follow-up respectively.

Conclusion
Multitarget thalamic and pallidal DBS proved to be the most effective therapy for this patient with secondary hemidystonia due to a putaminal stroke. A single-lead approach may not be sufficient in neuromodulating a highly disorganized motor network seen in hemidystonia. Multitarget DBS should be further explored in post-stroke dystonia and may offer improved outcome in other forms of secondary dystonia with limited response to GPi DBS.
Main Text

Introduction

In primary dystonia, the internal pallidum (GPI) is the most common target for deep brain stimulation (DBS) and provides good to excellent results in the majority of patients [1, 2]. In secondary dystonia, however, GPI DBS has a less impressive efficacy [3-5]. Alternative targets and multitarget stimulation have therefore been tried in these patients to improve results. One alternative target is the thalamus.

The Vim has historically been lesioned for dystonia and has recently been reinvestigated with Vim DBS in tardive dystonia [6, 7]. Thalamic lesioning and DBS in some studies has been shown to be more effective in patients with secondary dystonia [8-11]. We therefore undertook a prospective, randomized, blinded study to compare the outcome of GPI DBS versus Vim/Vop DBS versus simultaneous stimulation of both targets – multitarget DBS - in a case of stroke-induced hemidystonia. GPI DBS is thought to influence dystonia via modulation of the striato-pallido-thalamo-cortical pathways. The Vim/Vop area was chosen as it is part of the cerebello-thalamo-cortical network suspected to also be involved in the pathophysiology of hemidystonia [12].

The literature on thalamic surgery can be difficult to interpret due to the different nomenclatures used to describe the nuclei [18]. We will use Hassler’s thalamic nomenclature and the Schaltenbrand and Wahren stereotactic atlas [18, 19].

Methods

Three years after a left putaminal stroke due to a heart aneurysm at age six, the patient developed a right-sided hemidystonia. At age 22, she remained disabled by her condition despite medical treatment and botox therapy and was therefore considered a candidate for DBS. In light of the limited response to GPI DBS in these patients reported in the literature and in our experience, it was decided to test multitarget thalamic and pallidal stimulation. Hereafter, we will use the term multitarget DBS to describe simultaneous DBS in two different nuclei within the same hemisphere. This is to be distinguished from multiple electrodes within the same nucleus, which could be called multifocal DBS or simultaneous stimulation of the same nucleus in both hemispheres - commonly called bilateral DBS.

Institutional Review Board ethics was obtained to conduct this study in a blinded and randomized fashion. Left Vim/Vop (Medtronic 3387) and posteroverentral GPI (Medtronic 3389) DBS electrodes were implanted and connected to an implantable neurostimulator (Medtronic Activa PC). Post-operative imaging confirmed the deepest pallidal contact was at x=-20, y=+2, z=-4 relative to the midcomissural point. The deepest thalamic contact was at x=-13, y=-6, z=0 in the Vim with a shallow ring angle of 55° that kept the more proximal contacts within Vop. Figure 2 shows the location of the implanted electrodes on a post-operative CT merged to a pre-operative MRI.

Programming began one month later and was blinded to both the patient and examiner. The pallidal lead configuration was set to single bipolar: case off, contacts 0-, 1+, 2 off, 3 off (distal to proximal). Pallidal stimulation parameters were 185 Hz, 90µs, and 4.0 V. The thalamic lead configuration was set to wide bipolar: case off, 8+, contact 9 & 10 off, and 11-. Thalamic stimulation parameters were 185 Hz, 60 µs, and 4.0 V. Each combination of stimulation (GPI only, Vim/Vop only, GPI + Vim/Vop) was tested in a randomized and double-blinded manner.

After 3 months of stimulation in each setting, the BFMDRS and SF-36 were completed. A follow-up unblinded assessment of BFMDRS and SF-36 after six months of multi-target stimulation was added to the analysis.
Results
Vim/Vop or GPi stimulation alone slightly improved reported quality of life and was felt by the patient to be subjectively better than their baseline but did not result in improvement of dystonic movement as rated by the BFMDRS. Vim/Vop stimulation resulted in a higher increase in SF-36 compared to GPi stimulation; this was attributed to a significant reduction in the patient’s overall pain level.

Multitarget (Gpi + Vim/Vop) stimulation was preferred by the patient and resulted in the best functional improvement measured by the BFMDRS and the highest improvement in quality of life as measured by the SF-36. Additionally a decrease of her dystonia related pain was reported by the patient compared to baseline. Based on the results of the blinded trial, multitarget stimulation was chosen as the final setting. Six month follow-up data showed continued benefits regarding the BFMDRS and a slight reduction in SF-36 compared to early Gpi+Vim/Vop stimulation. Final stimulation parameters at the 6-month follow-up for multi-target stimulation did not change for the Vim/Vop target. Pallidal lead configuration and frequency (185 Hz) did not change; while stimulation voltage was adjusted from 4.0V to 4.5V and pulse width changed from 90 μs to 120 μs.

Multitarget DBS specifically improved the dystonia in her right limbs. Dystonic posturing of the right upper limb above her head stopped. The patient reported decreased pain and cramping, especially in her right shoulder and foot. Furthermore, headaches were less frequent and the right ankle was more flexible. The patient’s quality of life improved by 86% and 59% during the Gpi + Vim/Vop simultaneous stimulation trial and at the 6 month follow-up respectively. The Burke-Fahn Marsden Disability Scale (BFMDS) and Short-Form 36 (SF-36) quality of life data outcome measures are provided in Table 1. The location of electrode placement is provided in Figure 1.

Discussion
The best improvement in dystonic symptoms and quality of life for this patient with stroke-induced hemidystonia was seen following multitarget thalamic and pallidal DBS compared with stimulation of either target alone. The clinical benefit of multitarget DBS in this case raises questions about the mechanisms underpinning secondary dystonia and how best to treat it.

fMRI studies have found that patients suffering from hemidystonia have altered patterns of basal ganglia connectivity when compared to healthy subjects. [12] These changes include both a decrease of connectivity in some networks and a marked increase in others. Specifically, hemidystonia was associated with decreased activation in the contralateral thalamus, globus pallidus, and medial temporal cortex with dystonic arm task execution. In the ‘hypokinetic’ hemidystonic group, widespread bilateral over-activity was observed. [12]

Many of the effects seen are thought to be compensatory mechanisms all playing an active role in the development of secondary dystonia. The delayed onset commonly observed in secondary dystonia (and present in our case) is indirect evidence of maladaptive neural plasticity taking place [14]. The pathophysiology of dystonia appears to involve abnormalities in sensory function, loss of intracortical inhibition, and changes in plasticity within the sensorimotor cortex. [21]

Hemidystonia, however, can be seen in patients with lesions somewhere in either the cortico-striato-pallido-thalamo-cortical pathways or the cerebello-thalamo-cortical pathways and there is a growing body of evidence suggesting brain regions other than the basal ganglia are clearly involved in the etiology of dystonia [12]. Dystonia more likely has to be interpreted as a network disorder or a disease caused by “defective interactions among different nodes in a motor network, rather than a defect in motor pathways” [15, 16].
The minor effect of either single target stimulation in this trial suggests that both the cerebello-thalamo-cortical and the striato-pallido-thalamo-cortical pathways participate in the network disorder of post-putaminal stroke dystonia and that both nodes of this network need to be modulated for optimum clinical benefit.

An electrode within the GPi could influence the cortico-striato-pallido-thalamo-cortical network but might not influence the cerebello-thalamo-cortical pathway (and vice-versa for an electrode in the Vim/Vop). Since both pathways appear to be involved in the pathophysiology of this type of dystonia both pathways may need to be treated. Using the multitarget DBS approach we present, both electrodes are likely acting in a complimentary way in modulating cortical activity.

The role of the cerebellar pathways in dystonia has been discussed recently and the Vop is believed to be involved in the cerebello-thalamic connectivity (whereas Voa is more involved in pallido-thalamic pathways) [16]. In their publication on DBS for focal hand dystonia in the Voa/Vop area, Goto et al. did not find a clear difference in outcome compared to GPi stimulation and their questions whether Voa or Vop stimulation is the effective component of thalamic DBS remained unsolved.

We targeted the Vim/Vop area with the deepest contact (anode) in the Vim region. The cathode was chosen as proximal as possible to put current through the Vop. The electrical stimulation did not spread posteriorly into the VC nucleus, as the patient did not experience paresthesia. Current may have spread anteriorly to the Voa nucleus but this cannot be definitively confirmed; it is possible that this pallidal outflow relay nucleus may have been affected by thalamic stimulation. Nevertheless, it is clear that the addition of direct pallidal stimulation improved the patient’s clinical outcome more than just with thalamic stimulation alone.

The concept of simultaneous stimulation of multiple functional targets is not limited to one hemisphere: bilateral GPi DBS has recently been described to result in improved outcome compared to unilateral stimulation in a case of striatal stroke induced hemidystonia [17]. This is not surprising since changes in interhemispheric motor circuitry connectivity have also been described in secondary dystonia [13,14].

Secondary dystonia is a heterogeneous disorder with respect to its cause and clinical presentation and different types of secondary dystonia may require individualized treatment [20]. The mechanism of dystonia induction by putaminal stroke is most likely unique and whether multitarget DBS delivers reproducible results in other forms of secondary dystonia or even in secondary dystonia caused by stroke in locations other than the putamen remains unclear at this time. In the past, the thalamus was regarded as an advantageous avenue to target in secondary dystonia; this was prior to the validation of posteroventral lateral GPi as the best first-line target [21]. In the pre-DBS era, thalamotomies and subthalamotomies were employed to treat choreo-athetotic cerebral palsy and secondary dystonias, [21-23], but the choice of thalamic nucleus target was highly variable among surgeons.

Finally, the anatomy of the thalamus and basal ganglia is often distorted by the very insult (i.e-stroke) that causes secondary dystonia. We recommend that direct anatomical targeting may be the best method to accommodate this distortion. While this patient had targeting from internal landmarks (AC-PC line) with guidance from awake macroelectrode stimulation, our centre is moving towards direct anatomical targeting in future cases.

While it is the first double-blinded, randomized assessment of multitarget DBS in hemidystonia, the conclusions that can be drawn are limited by the fact that we report on a single case. Finally, it is important to appreciate that hemi-dystonia (and segmental dystonia) patients are typically less functionally impaired (as measured by the BFMDRS) compared to patients with primary dystonia. Thus,
their degree of functional improvement after surgery may appear smaller and not as dramatic. We believe this is important recognize when interpreting results in the literature regarding hemi-dystonia. Other scales such as quality of life and modified dystonia scales should be relied on to account for this inherent limitation.

**Conclusion**
Multitarget (Vim/Vop + GPi) DBS proved to be the most effective therapy for this patient suffering from secondary, childhood onset hemidystonia due to a putaminal stroke. Using a single-lead approach may not be sufficient in neuromodulating a highly disorganized motor network seen in hemidystonia patients. We believe that multitarget DBS in different nuclei requires further investigation for secondary dystonia with limited response to GPi DBS. The recent emergence of dystonia being interpreted as a “network disorder” warrants this exploration.
Acknowledgements
None

Authors’ roles
CRH designed the study, performed DBS implantation and critically revised the final manuscript. AP collected /analyzed data and revised the final manuscript, PJS analyzed data and wrote the manuscript draft. All authors approved the final version of the manuscript.

Financial Disclosures
CRH has received speaking honoraria and consultation fees from Medtronic. PJS and AP declare no conflicts of interest.
Table 1 Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) and SF-36 quality of life measured pre-operatively, after three-months of stimulation in each setting, and at six-month follow-up with multitarget stimulation. Score and percentage improvement from baseline provided.

<table>
<thead>
<tr>
<th></th>
<th>BFMDRS (%) Improvement</th>
<th>SF-36 (%) Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Operative</td>
<td>24</td>
<td>45</td>
</tr>
<tr>
<td>GPI stimulation</td>
<td>24 (0%)</td>
<td>54 (15%)</td>
</tr>
<tr>
<td>Vim/Vop stimulation</td>
<td>24 (0%)</td>
<td>66 (46%)</td>
</tr>
<tr>
<td>GPI+Vim/Vop stimulation</td>
<td>18 (25%)</td>
<td>81 (86%)</td>
</tr>
<tr>
<td>6 month follow-up GPI+Voa/Vop</td>
<td>18 (25%)</td>
<td>76 (59%)</td>
</tr>
</tbody>
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Figure 1- Location of electrodes is shown with a post-operative CT (windowed to show metal) merged to a pre-operative MRI (T1 with gadolinium). A. Axial image 4mm below AC-PC line shows electrode in GPi (long arrow). B. Axial image at AC-PC shows electrode in Vim (short arrow). Artifact of GPi electrode (long arrow) is seen passing just medial to the area of putaminal stroke.
References


