Clinical Research

Evaluation of the efficacy of deep brain stimulation in the surgical treatment of cervical dystonia

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ABSTRACT

Objective: Deep brain stimulation (DBS) of the globus pallidus internus (GPI) is a promising therapeutic option for patients with medically refractory dystonia. We present the results after 1 year of DBS of the GPI in 4 patients with cervical dystonia.

Materials and methods: Four patients with medically refractory cervical dystonia who underwent stereotactic pallidal DBS surgery between June 2010 and November 2011 were included in this retrospective study. Preoperative and postoperative evaluations at 3, 6 and 12 months after surgery were performed using the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS).

Results: The 4 patients experienced a sustained improvement, with a mean TWSTRS reduction of 74.25%, at 12 months follow-up. Disability improved by 80.5% (mean) at 1 year follow-up. No stimulation-related side effects were reported.

Conclusion: Pallidal DBS is a valid and effective second-line treatment for patients with cervical focal dystonia. Our results support its use in patients with an insufficient response to medical treatment.

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Evaluación de la eficacia de la estimulación cerebral profunda en el tratamiento quirúrgico de distonía cervical

RESUMEN

Objetivo: La estimulación cerebral profunda (ECP) del globo pálido interno (GPI) es una terapéutica eficaz para pacientes con distonía refractaria al tratamiento médico. Presentamos 4 pacientes con distonía cervical refractaria operados con ECP utilizando como diana el GPI y los resultados un año después de la cirugía.

Material y métodos: Fueron incluidos en este estudio retrospectivo 4 pacientes con distonía cervical refractaria al tratamiento médico que fueron sometidos a cirugía estereotáctica para ECP del GPI entre junio 2010 y noviembre 2011. Fueron realizadas evaluaciones pre y postoperatorias a los 3, 6 y 12 meses utilizando la escala Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS).

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**Introduction**

Dystonia is a chronic disease that has a major impact in life quality.

Dystonia is a chronic disease that has a major impact in life quality.\(^1\)\(^-\)\(^3\) It represents one of the most painful and disabling movement disorders consisting of repetitive, sustained and involuntary contractions of both agonist and antagonist muscles, that leads to abnormal postures, twisting and patterned movements.\(^1\)\(^-\)\(^4\) Dystonia also manifests during voluntary movements through the activation of additional muscles, usually not requested for the purposes of movement.\(^1\)\(^-\)\(^2\)

Several scales have been purposed to classify dystonia, according to etiology (primary and secondary), age of onset (early-onset and adult-onset), and affected muscles groups (focal, segmented, multifocal, hemidystonia and generalized).\(^3\)\(^-\)\(^6\)

Despite being a common movement disorder, uncertainties about dystonia pathology remain since the number of human dystonia cases that have been studied for neuropathological mechanisms is reduced.\(^5\)

It is believed that all dystonias implicate a final neurological pathway of diminished thalamocortical output, allowing for simultaneous activation of opposing muscles.\(^4\)

Although it is not usually associated with diminished cognitive abilities or life span, there are rare complications that one must be aware of such as hyperthermia, rhabdomyolysis, myoglobinuria, respiratory failure and dystonic storm or status dystonicus.

So far there is no cure for dystonia and available treatments are symptoms directed.\(^7\)

Botulin-toxin EMG-guided chemodenervation is the gold standard therapy for cervical idiopathic dystonia\(^8\)\(^-\)\(^10\) and both botulinum toxins A and B are approved for cervical dystonia treatment.\(^11\)\(^-\)\(^12\) Trihexyphenidyl, benzodiazepines, tetrabenazine, cyclobenzaprine, carbamazepine and oral baclofen are also approved for the treatment of cervical dystonia. Despite these options, with the exception of dopa-responsive dystonia, pharmacological treatment is usual unsatisfactory, with patients experiencing little or no symptom relief at all.\(^5\)\(^-\)\(^6\)

Neurosurgical techniques, such as pallidotomy and thalamotomy, concern permanent lesioning of basal ganglia, are being replaced for DBS. The irreversibility and non-adjustable characteristic are some of the disadvantages of these ablative surgeries. Permanent cognitive adverse effects, as well as speech and swallowing impairments, are frequent findings after bilateral lesioning of basal ganglia.\(^6\)\(^,\)\(^11\)

**DBS**

Among the available surgical options, pallidal DBS is currently the most effective treatment for medically refractory dystonia, having replaced pallidotomy and thalamotomy that were associated with neurologic disabling side effects.\(^6\)\(^,\)\(^13\)\(^,\)\(^14\)

Although DBS mimics lesioning procedures, it is reversible and neurostimulation variables are adaptable.\(^12\)\(^,\)\(^15\)

Current issues in dystonia DBS treatment include response variability and predictors, patient selection, timing and standardized programming settings.

It is widely accepted that DBS is an effective option to treat focal and generalized primary dystonia. However, it remains unclear whether pallidal stimulation is also effective in the treatment of secondary dystonias.\(^11\)

In DBS surgery, the device is usually implanted in two stages. In the first one, the quadripolar lead electrode is implanted stereotactically into the Globus pallidus internus. This can be performed with the patient awake, which allows for a more precise location of the lead, although it may not be possible with children or patients with severe dystonic postures.\(^11\)\(^,\)\(^16\)

In the second stage, the pulse generator is implanted in the chest wall and the extension cable is implanted connecting the lead to the pulse generator. These two stages could be done in the same operative time.

Regarding the stimulus provided by the DBS device, four parameters can be adjusted: amplitude, pulse width, frequency and choice of the active contacts.

Optimal settings in the treatment of dystonia are unknown. Some studies report positive outcomes with wide pulses (210–400\(\mu\)s) and high frequencies (130 Hz or higher), and others have found good results with lower settings (60–80 Hz; 210\(\mu\)s), as well as a less frequent need to replace the battery.\(^11\)

Regarded as a promising surgical option in cervical dystonia, more data are needed to improve and predict outcomes.\(^5\)\(^,\)\(^13\)

The only contraindications to DBS surgery may be severe psychiatric disease, cognitive disability or other psychosocial circumstances that would impair the necessary close follow-up for programming and maintenance of the device.\(^5\)\(^,\)\(^11\)

As previously mentioned for pharmacological treatment, DBS is a symptomatic treatment, not a treatment aimed at etiologic mechanisms, although these remain the ultimate objective toward the cure of dystonia.

The objective of this study is to evaluate the efficacy of pallidal DBS in the treatment of medically refractory cervical dystonia.
Materials and methods

We obtained institutional ethics committee review and approval for this study.

The study took place at Neurosurgery Department of Centro Hospitalar de S. João, in Porto, Portugal, between July 2010 and March 2013.

Four patients were consecutively recruited. Inclusion criteria were clinically diagnosed cervical dystonia, pharmacological treatment failure, having been submitted to DBS surgery for focal idiopathic dystonia, between June 2010 and November 2011, no secondary cause for dystonia, no other changes besides dystonia on neurological examination, normal findings on cerebral magnetic resonance imaging (MRI), and absence of cognitive and psychiatric disturbances.

All patients were injected with botulinum toxin (both toxin A and B) into the affected muscles. The four experienced primary failure or diminished response and insufficient relief from botulinum toxin over time.

One patient had early onset dystonia (<28 years) and hand tremor.

Table 1 summarizes the demographic characteristics of the patients in our study.

By the time of DBS surgery, the mean age of patients was 46.25 years (SD ± 11.47). The mean age at the onset of disease was 38.5 years (SD ± 15.61), and the mean duration of symptoms before surgery was 7.75 years (SD ± 5.12).

Drugs for treatment of dystonia at the time of surgery included trihexyphenidyl, baclofen, benzodiazepines, antidepressants, analgesics and physiotherapy.

To evaluate patients clinical response the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) was applied at baseline (preoperatively) and at 3, 6 and 12 months of follow-up. The TWSTRS subscales of severity and disability were applied. Patients were filmed and evaluated by the same physician, a neurologist consultant of our movement disorders unit.

The same surgical team carried out DBS surgery in all four patients, at Centro Hospitalar de S. João. All patients were operated bilaterally in GPI and the preliminary target for electrodes implantation was defined by stereotactic CT fused with a volumetric MRI. For the GPI planning the MRI sequences used were volumetric MPRAGE with Gad double dose 0.4 ml/kg FOV280, isotropic voxel 0.9 TR1200, TE 3.61, and a DP and T1IR FOV 280, contiguous 2 mm slices without GAP, TR 3360 TE 14 (DP) and TR 3330 TE38 (IR). The target was chosen using the atlas-based coordinates and lies 2 mm in front of the midcommissural point, 20–22 mm lateral from the midline of the third ventricle and 3–6 mm ventral to the AC-PC line and corrected with direct visualization of the MRI (Fig. 1).

The patients were operated under balanced general anesthesia induced with propofol and maintained with sevoflurane and fentanyl. BIS (bispectral index) was maintained above 60 during macrostimulation. The patient is in semi sitting position. An arctiform incision is made about 1 cm in front of the coronal suture and 2–3 cm lateral to sagittal suture. A 13 mm burr-hole was done and 3 microelectrodes were placed. Microrecording was performed to achieve GPI, followed by macrostimulation to assess capsulation. Typical structures encountered along a recording tract during the implantation of GPI electrodes include the corona radiata, striatum (caudate/putamen), lateral medullary lamina, GPe, medial medullary lamina, GPI, accessory medullary lamina (or lamina pallidi incompleta), GPI, ansa lenticularis, and optic tract, which is located ~2 mm ventral to the border of the GPI (Fig. 2).
The electrode immediately lateral was chosen. Also visual phenomena were evaluated concerning the depth of the tip of the electrodes. The definitive electrode was then implanted under fluoroscopic control. The surgical procedure of tunneling the DBS extensions was performed as previously described by the same group.37 Fig. 3 illustrates electrodes implanted on post-operative CT scan. Postoperative CT fusion with pre-operative MRI allowed assessment of electrodes.

Although stimulation settings were not an issue on this study, settings at the last follow-up are specified in Table 2.

Results

Results are presented as mean (±standard deviation).

Percent of benefit was calculated with the formula [(TWSTRS score at baseline – TWSTRS score postoperatively)/TWSTRS score at baseline] × 100.

Data shown concern TWSTRS severity subscale (Table 3) and disability subscale (Table 4).

Both severity and disability scores were significantly reduced in all patients since the beginning of follow-up.

Three months after surgery, the mean improvement in severity was 71.75%. Patients experienced an 81.5% improvement in disability scores, at 3 months follow up.

Table 1 – Demographic features of patients in this study.

<table>
<thead>
<tr>
<th>No</th>
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<th>Age at surgery (years)</th>
<th>Age at onset of dystonia (years)</th>
<th>Duration of disease (years)</th>
<th>Medical therapy</th>
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<tr>
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<td>45</td>
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<td>DZP, CZP</td>
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<td>18</td>
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<td>BPP, DZP, THP, VFX, DZP</td>
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<td>4</td>
<td>Female</td>
<td>51</td>
<td>40</td>
<td>11</td>
<td>MRP</td>
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</table>

DZP, diazepam; CZP, clonazepam; EAC, baclofen; GBP, gabapentin; APZ, alprazolam; THP, trihexyphenidyl; BPP, bupropion; VFX, venlafaxine; MRP, morphine sulfate.
Fig. 1 – Pre-operative magnetic resonance imaging planning depicting chosen targets and pathways to GPI stimulation.

<p>| Table 2 – Stimulation settings after bilateral GPI – DBS. |
|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>No</th>
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<th>Pulse width (μs)</th>
<th>Mean amplitude (V)</th>
<th>Impedance (W)</th>
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<td>60</td>
<td>3</td>
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</tbody>
</table>

GPI, globus pallidus internus; DBS, deep-brain stimulation.

<p>| Table 3 – Toronto Western Spasmodic Torticollis Rating Scale severity subscores. |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>No</th>
<th>TWSTRS baseline</th>
<th>TWSTRS at 3 months</th>
<th>Severity benefit at 3 months (%)</th>
<th>TWSTRS at 6 months</th>
<th>Severity benefit at 6 months (%)</th>
<th>TWSTRS at 12 months</th>
<th>Severity benefit at 12 months (%)</th>
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<td>7</td>
<td>72</td>
<td>7</td>
<td>72</td>
<td>7</td>
<td>72</td>
</tr>
<tr>
<td>Mean</td>
<td>22.5</td>
<td>6.25</td>
<td>71.75</td>
<td>6.5</td>
<td>70</td>
<td>5.5</td>
<td>74.25</td>
</tr>
</tbody>
</table>

(2.65) | (0.96) | (6.6) | (2.89) | (16.99) | (3.87) | (20.66) |
Fig. 2 – Electrophysiological recordings on the way toward demarcation of the sensorimotor area of the globus pallidus internus (GPI). Insertional activity from recordings in the putamen at −6.0 mm; lateral medullary lamina; GPe at −3.5 mm; medial medullary lamina; border cells at −2.0 mm; GPI starting at −1.5 mm; probable accessory medullary lamina and GPI again at 0.5 mm.

At 6 months follow-up, both severity and disability scores were slightly higher, with correspondent lower severity and disability improvements: 70% and 76.5%, respectively.

However, at 12 months follow-up, both severity and disability scores improved. The four patients experienced sustained severity improvement by a mean of 80.5%, at 12 months follow-up. At one year follow-up, the disability benefit improved by 74.25% (mean).

Three patients had pain in the pre-operative period (grades 4, 4 and 5) that disappeared after stimulation. One patient had no pain before surgery and remained painless thereafter. We have not experienced any case of bradykinesia after motor GPI stimulation.

There were no perioperative complications in all four surgeries.

Discussion

Until the late 1990s, regarding cervical dystonia treatment, DBS was considered a third-line option, after botulinum toxin injections and surgical peripheral denervation of the affected muscles. Since the introduction of DBS by Krauss and coworkers the confirmation of sustained benefit in dystonia treatment was observed in several studies.12,19-22 Loss of benefit from DBS after one year is rare,6 meaning that DBS is now a valid and safe first-line treatment for cervical dystonia.9

The precise mechanism by which pallidal stimulation modulates dystonia is unknown. It is believed that DBS alters both neuronal discharge as well as axonal propagation, functionally

Table 4 – Toronto Western Spasmodic Torticollis Rating Scale disability subscores.

<table>
<thead>
<tr>
<th>No</th>
<th>TWSTRS baseline</th>
<th>TWSTRS at 3 months</th>
<th>Disability benefit at 3 months (%)</th>
<th>TWSTRS at 6 months</th>
<th>Disability benefit at 6 months (%)</th>
<th>TWSTRS at 12 months</th>
<th>Disability benefit at 12 months (%)</th>
</tr>
</thead>
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<td>89</td>
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<td>73</td>
<td>4</td>
<td>73</td>
<td>4</td>
<td>73</td>
</tr>
<tr>
<td>Mean</td>
<td>15</td>
<td>2.75</td>
<td>81.5</td>
<td>3.5</td>
<td>76.5</td>
<td>2.75</td>
<td>80.5</td>
</tr>
<tr>
<td></td>
<td>(2.94)</td>
<td>(4.92)</td>
<td>(16.09)</td>
<td>(2.08)</td>
<td>(15.15)</td>
<td>(2.75)</td>
<td>(19.33)</td>
</tr>
</tbody>
</table>
modifying the aberrant motor pathways, leading to a normalized motor response. DBS surgery has a low rate of complications. These can be intraoperative hemorrhage or ischemia, perioperative infection, requiring of device removal, and displacement or fracture of the extension cable. Sometimes, lead fracture can occur, more frequently than in Parkinson’s or tremor’s patients, due to vigorous dystonic movements. In the rare case of inadequate response, lead repositioning may be necessary. 

So far, concerning cognitive and neuropsychiatric effects, no adverse outcomes have been described. Our study shows that patients with cervical dystonia with previous medical failure including botulinum toxin injections may achieve sustained improvement after pallidal stimulation. Like in other studies, gradual increase in benefit occurs and may take several months to reach the maximum benefit although this may not necessarily be true for all patients. Some evidence points to the maintenance of DBS benefit even after suspension of pallidal stimulation. One patient with cervical dystonia, treated with DBS for 5 years, showed sustained improvement for 6 months after discontinuation of pallidal stimulation. There is a similar report for a patient with cranial dystonia. This evidence suggests that in focal dystonia DBS may permanently correct the abnormal motor pathways. A limitation of our study is the small number of patients, which does not allow us to assert new conclusions. However all patients had cervical dystonia, creating a homogeneous group of patients.

Despite the reduced number of participants, outcomes at 12 month follow-up were similar to that published by other groups. Loher et al. found a mean severity improvement of 55% and a 66.8% disability benefit (mean), at one year follow-up. Ostrem et al. found a severity improvement of 43.5%, and a disability benefit of 70.8%. Krauss et al. found a mean improvement of 63% in both severity and disability, with a longer follow-up (20 months). In our group of patients we found mean improvements in severity and disability scores of 74.25% and 80.5%, respectively. Another study by Kiss et al. found smaller improvements: 43% benefit in severity scores and 24% improvement in disability. Despite a large number of successful reports, the criteria for chronic DBS remain empirical. The variability of response to pallidal stimulation reflects the lack of recognition regarding patient selection and clinical outcome predictors. To this moment, no possible predictive factors have been established, but data point to lower preoperative severity score, younger age at surgery, positive DYTI mutation, shorter duration of disease and the lack of skeletal deformities as possible predictive factors.

It is important to perform the surgery before the occurrence of definitive orthopedic abnormalities that will limit the functional benefit achieved with the DBS surgery. The experience of the surgical team, the precise lead placement and the correct device programming all contribute to achieve good outcomes.

Concerning children, DBS has been performed safely, and with positive outcomes, in an increasing number of pediatric patients. Pallidal stimulation is appropriate for a developing brain and should therefore be considered a safe therapeutic option for children presenting with severe, medically refractory dystonia. Positive outcomes have also been reported in the treatment of severe tardive dystonia, myoclonus–dystonia and status dystonicus. Due to the severity of status dystonicus, a life-threatening condition that must be solved promptly, DBS is an acute therapeutic option.

One strength of our study is the fact that the same surgical team performed the DBS surgery in all four patients, with the outcomes being evaluated by the same physician at the same hospital facilities.

The application of a known validated scale, the TWSTRS, to assess severity and disability scores at baseline, as well as clinical outcomes after DBS surgery allows us to trust our results.

We could not find any relationship between the duration of disease and the improvement achieved. In our patients, those with a longer duration of disease (patients no 3 and 4) had high improvement scores, both in severity (96% and 72%, respectively) and disability (92% and 73%, respectively). Due to the variability of scores as time passes by, it would be helpful to evaluate patients for a longer period in order to understand when do the improvements stabilize.

In our study we did not evaluate the stimulation settings, so no prognosis factors were identified. However, one patient needed to adjust stimulation settings (from GPI left: 3.2 V/60 µs/130 Hz, impedance 1278ω; GPI right: 2.5 V/60 µs/130 Hz, impedance 700ω, to GPI left: 3.2 V/60 µs/130 Hz, impedance 1133ω; GPI right: 3 V/60 µs/130 Hz, impedance 972ω), suggesting that these variables play an important role in cervical dystonia treatment with DBS.

**Conclusion**

This study demonstrated that pallidal stimulation allows for a sustained decrease in the severity of cervical dystonia. DBS also results in frank improvements in disability resulting from this movement disorder, and the rate of complications is considerably small. Therefore, pallidal DBS must be considered a safe, valid and successful surgical therapeutic option for cervical dystonia.

**Conflict of interest**

The authors have no conflict of interest to declare.

**REFERENCES**