The Canadian multicentre study of deep brain stimulation for cervical dystonia

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Deep brain stimulation (DBS) of the globus pallidus pars interna (GPi) is an effective treatment for generalized dystonia. Its role in the management of other types of dystonia is uncertain. Therefore we performed a prospective, single-blind, multicentre study assessing the efficacy and safety of bilateral GPi-DBS in 10 patients with severe, chronic, medication-resistant cervical dystonia. Two blinded neurologists assessed patients before surgery and at 6 and 12 months post-operatively using the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS). The primary outcome measure was the severity subscore (range 0–30, higher scores indicating greater impairment). Secondary outcomes included disability (0 to 30), pain (0 to 40) subscores and total scores of the TWSTRS, Short Form-36 and Beck depression inventory. Swallowing and neuropsychological assessment were also performed at baseline and 12 months. One-way repeated measures analysis of variance was used to analyse the data.

The TWSTRS severity score improved from a mean (SD) of 14.7 (4.2) before surgery to 8.4 (4.4) at 12 months post-operatively (P = 0.003). The disability and pain scores improved from 14.9 (3.8) and 26.6 (3.6) before surgery, to 5.4 (7.0) and 9.2 (13.1) at 12 months, respectively (both P < 0.001). General health and physical functioning as well as depression scores improved significantly. Complications were mild and reversible in four patients. Some changes in neuropsychological tests were observed, although these did not impact daily life or employment. Our results support the efficacy and safety of GPi-DBS for the treatment of patients with severe and prolonged cervical dystonia who have failed medical management.

Keywords: dystonia; torticollis; deep brain stimulation; clinical trial; globus pallidus; high-frequency stimulation

Abbreviations: BDI = Beck depression inventory; DBS = deep brain stimulation; MRI = magnetic resonance imaging


Introduction

Deep brain stimulation (DBS), a reversible and safe surgery used to treat movement disorders since the 1990s, has recently been reported to improve generalized dystonia (Coubes et al., 2000; Tronnier and Fogel, 2000; Vidalilhet et al., 2005). Stimulation of the globus pallidus pars interna (GPi) for cervical dystonia was first reported in 1999 (Krauss et al., 1999) and was followed by several case reports and small series (Kulisevsky et al., 2000; Krauss et al., 2002). However case series often combined multiple different dystonia types (Berezni et al., 2002; Krauss et al., 2002; Yianni et al., 2003; Eltahawy et al., 2004a, b; Bittar et al., 2005), and the ability to draw conclusions was limited by variations in selection criteria, use of validated clinical scoring methods, unblinded outcome measures (Hung et al., 2007), the same patients reported more than once, and short duration of follow-up (Krauss et al., 1999; Islek et al., 1999). Therefore, we conducted a prospective, multicentre pilot study to determine the effect of bilateral pallidal DBS on severity, disability, pain and quality of life in patients with cervical dystonia, using standardized and blinded measures.

Materials and methods

Each site obtained institutional ethics committee review for this study and each patient provided informed consent. This pilot project was registered with NIH ClinicalTrials.gov (NCT00132990).
Patients
Ten patients were consecutively recruited at five academic centres in Canada. Inclusion criteria were clinically diagnosed cervical dystonia for at least 5 years; initial response and subsequent failure of botulinum toxin A and/or B injections; no secondary cause; a normal neurological examination except for dystonia; normal findings on magnetic resonance imaging (MRI) of the brain; the absence of psychiatric disturbances; normal cognitive function, as reflected by neuropsychological assessments. Patients with generalized dystonia were excluded.

Study design and outcome measures
The primary outcome measure was the severity subscale of the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), as assessed by two blinded neurologists. The TWSTRS is a validated and widely utilized scale (Consky and Lang, 1994; Comella et al., 1997) consisting of three sections: severity (range 0–30), disability (range 0–30) and pain (range 0–40), with higher scores indicating greater impairment. Severity was judged on the basis of standardized videotapes and disability and pain assessed by means of patient questionnaires. Secondary outcomes included the TWSTRS subscores for pain and disability, the Beck depression inventory (BDI) (Beck, 1997), ShortForm-36 (SF-36) to measure quality of life (Ware and Sherbourne, 1992), global assessment of change and adverse events.

The TWSTRS and other assessments were performed at baseline (at least 3 months after the last botulinum toxin injection, if patients were still receiving it), 6 months and 12 months post-operatively. Follow-up was measured as time from implantation of pulse generator. At the completion of the study all 30 videotapes were randomized and scored by two neurologists blinded to patient name and time of assessment. Severity scores were then averaged. Additional visits occurred at 3 months after surgery to determine early adverse events. Swallowing studies and neuropsychological assessments were performed pre-operatively and at 12 months follow-up. Neuropsychological assessments were performed as per routine in each centre; neither the tests nor the normative data were standardized across centres.

Surgery
All centres had significant experience in GPi brain mapping and DBS surgery. The initial implantation target was 2 mm anterior to, 19–21 mm lateral to and 2–6 mm below the midcommissural point; the final implantation site was further refined by a combination of direct visualization on MRI, microelectrode recordings, and intraoperative stimulation (as per local practice). Firing rates of GPi neurons were slightly lower than those reported for Parkinson’s patients (Tang et al., 2007). However, the overall pattern of recordings passing from anterodorsal to posteroventral (very low frequency firing cells in the putamen, mid frequency firing in the globus pallidus pars externa and the highest firing rates in the GPi), similar to that seen in Parkinson’s disease patients, was maintained (Kiss et al., 2004b). DBS leads were implanted bilaterally in one or two sessions with the patient under local anaesthesia with or without sedation. In three centres (N=6 patients) microelectrode recordings were used to perform the brain mapping (Lozano et al., 1996), whereas in two centres (N=4 patients) macrostimulation alone was utilized (Laitinen et al., 1992). Macrostimulation was performed to map the posteroventral GPs, as previously described for pallidotomy (Honey and Nugent, 2000). After brain mapping the quadripolar DBS electrode (3387, Medtronic, Minneapolis, USA) was implanted and either immediately or several days later, connected to a neurostimulator (Kinera, Medtronic, USA) implanted in the subclavicular region under general anaesthesia.

All patients underwent post-operative MRI to confirm correct electrode placement and to assess for surgical complications. MRIs were not standardized with respect to imaging sequences, but performed as per routine at each centre. Images were checked by two neurosurgeons from another centre, blind to patient outcome and centre. Each neurosurgeon independently decided whether each electrode was adequately positioned in the posteroventral GPi, or whether an electrode was too medial/lateral, dorsal/ventral or anterior/posterior.

Programming was performed as was customary in each centre: by nurse specialists in four hospitals and a neurosurgical fellow in the fifth centre. Initially programming was performed as recommended by previously published work (Kumar, 2002); however, after the lead centres initial experience (Kiss et al., 2004b), we recommended not waiting more than 1 week before altering programming parameters, in case of insufficient improvement. Programming commenced using monopolar stimulation trying each pole in sequence, with a pulse width of 210 µs and frequency 180 Hz, with subsequent changes in voltage, frequency, pulse width and polarity to optimize clinical benefit. If monopolar stimulation produced adverse effects, bipolar stimulation was subsequently tested.

Statistical analysis
Data are shown as mean±SD. Percent change was calculated using the formula (pre-op score – 12 month post-op score)/pre-op score. One-way repeated measures analysis of variance was used to compare 6-month and 12-month outcome scores to baseline pre-operative scores. Post hoc comparisons were performed using Dunnett’s test. All tests were two-tailed and results with P values <0.05 were considered to be statistically significant.

Results
Table 1 summarizes the clinical characteristics of the patients. The median age of the patients at surgery was 57.5 years (range 47–64). The median age at the onset of dystonia was 43 years (range 19–51), such that the median duration of the disease was 16.5 years (range 5–28). Five patients had prominent associated tremor, three had minimal tremor and two had no tremor at all. A mild head injury was reported as initiating the dystonia in one patient. Another patient had some writer’s cramp, which was mild and had not required treatment. Three patients had previous surgery, which was ineffective. These patients represented those who had the most severe symptoms and were most willing to try new procedures, despite having failed previous surgery.

The primary outcome measure, TWSTRS severity score (Fig. 1) improved from a mean (SD) of 14.7 (4.2) before surgery to 10.6 (4.8) at 6 months and 8.4 (4.4) at 12 months post-operatively (P=0.003). In comparison to
Baseline, both 6 and 12 month severity scores were significantly reduced.

Figure 2 shows similar results for the secondary outcomes. The TWSTRS disability and pain scores improved from 14.9 (3.8) and 26.6 (3.6) before surgery, to 5.4 (7.0) and 9.2 (13.1) at 12 months post-op, respectively \((P<0.001\) and \(P<0.001\), respectively). Beck depression scores improved from 14.2 (7.2) at baseline to 6.0 (3.5) at 12 months \((P<0.001\), Fig. 3A). Quality of life as measured by SF-36 improved from 90.9 (11.3) at baseline to 112.9 (18.0) at 12 months \((P=0.003\) (Fig. 3B).

All patients, treating neurologists and neurosurgeons scored the global assessment of outcome as ‘good’ or ‘very good’ improvement at the 12-month time point, except in one case. Patient 7 was discovered to be suffering from significant depression after surgery (despite scoring within acceptable range on the Beck depression inventory). After the depression was treated, she allowed the stimulator to be turned on, but nonetheless, her responses to stimulation were unusual and with blinded severity measurements, her dystonia worsened.

### Stimulation variables

This study did not dictate specific stimulation parameters to utilize at each centre. We suggested that each programmer follow published recommendations based on experience with generalized dystonia (Kumar, 2002), but starting with a pulse width of 210\(\mu\)s. After our initial experience (Kiss et al., 2004b), centres were instructed to wait no more than 1 week between programming sessions to determine the effects of stimulation. DBS frequency at 12 months was 170 (20) Hz, pulse width was 204 (49) \(\mu\)s and amplitude was 3.3 (0.7) V. Table 2 (Supplementary Material) reports the electrode poles utilized for each patient.
In case 2, described in our preliminary report (Kiss et al., 2004b), DBS programming initially produced no benefit for the first 3 months. At the 3-month post-surgery follow-up appointment, both the patient and programming nurse had concluded that DBS was not effective. Monopolar stimulation had been applied to the most dorsal electrode poles (3/7) bilaterally. At this delayed time point, stimulation was altered such that bipolar stimulation using the most ventral poles (poles 0/4, at 180 Hz, 180 μs pulse width) allowed an amplitude of 3.0 V to be reached without side effects. It resulted in an immediate improvement in subjective tightness of the neck and shoulder, followed by a gradual visible straightening of the head over the ensuing few days. One week after these settings were initiated, the patient displayed little residual torticollis (videos available from Kiss et al., 2004b). The time course of benefit for the other patients ranged from immediate improvement (as described earlier) to a requirement for several weeks (1–8 weeks) or even 6 months (one patient) of stimulation.

**Medical treatment**

Pre-operatively, eight patients were taking medication for their cervical dystonia, either for pain or the movement disorder itself (Table 1). All had initially responded but secondarily failed botulinum toxin A and/or B. After DBS surgery, no patient received further injections and most patients were able to reduce their pain or muscle relaxant drugs.
MR imaging
All patients underwent MR imaging post-operatively to confirm correct electrode placement and detect complications. Images were reviewed by the lead site neurosurgeon and another neurosurgeon blinded to patient outcome and centre. The only post-operative imaging complication was a small subdural fluid collection in a patient who remained asymptomatic (Supplementary Table 2). There was no obvious relationship between successful outcome and electrode placement. The only patient who deteriorated after surgery, had well-placed electrodes into both posterovenral GPi (Fig. 4).

Adverse events
Four adverse events occurred in four patients in the post-operative period; all resolved rapidly without permanent morbidity (Supplementary Table 2). One patient had dysphagia for the first few weeks post-operatively. This subsided with a decrease in stimulation amplitude, although it was detected on the modified barium swallow at 1 year. Another patient had dysarthria that also resolved with a change in stimulation parameters. One patient had a transient facial weakness immediately post-operatively that resolved before the 3-month visit. Another patient developed shingles in the left ophthalmic division of the trigeminal nerve, after her first side surgery; therefore her second side DBS implant was delayed by 1 month. A small chronic subdural fluid collection was seen at the second side surgery and drained during that procedure. This same patient had a very subtle hemiparesis (seen only on gait) that was present at 6-month follow-up, but resolved completely by 12 months.

Two patients had mild difficulties with swallowing and two others had mild improvements on swallowing tests. There were some changes seen on neuropsychological testing as detailed in Supplementary Table 2. Significant declines (as defined by ≥2 SD) were seen in two patients. In one patient this degree of decline was limited to phonemic fluency, and in the other patient it was limited to verbal memory. However, these changes along with the other smaller changes seen were not significant enough to impact daily life or working ability.

Discussion
Bilateral pallidal DBS in patients with primary cervical dystonia, led to a significant and sustained improvement in head and neck postures over a 1-year period. The mean improvement in dystonia severity was 43% compared with pre-operative scores. When combined with patient reported pain and disability scores, the total TWSTRS improved by 59%. There were significant improvements in quality of life (24%) and depression scores (58%), minor effects on swallowing and cognitive tests. Medications were reduced after surgery and no further botulinum toxin injections performed.

Our results, obtained from a prospective trial of patients meeting strict inclusion criteria, confirm results obtained in individual patients (Islekel et al., 1999) and small single site series (Krauss et al., 1999, 2002; Berezniak et al., 2002; Yianni et al., 2003; Eltahawy et al., 2004b; Bittar et al., 2005; Hung et al., 2007). In these previous published series, severity subscores improved by 48 (Krauss et al., 1999) to 63% (Krauss et al., 2002) and only one report failed to identify motor improvement (Kulisevsky et al., 2000). The largest case series in which 10 patients with isolated cervical dystonia were operated at a single centre, found 55% improvement in severity scores; however, these were obtained in a non-blinded fashion (Hung et al., 2007). It is not surprising that our results obtained from multiple centres, using blinded severity measurements are not quite as good as those reported from open-label series.

Instead our results are very similar to those reported by Kupsch et al. (2006) in which patients with generalized and segmental dystonia were randomized to active or sham neurostimulation. These authors found a 39% improvement in the motor score using the Burke–Fahn–Marsden Dystonia Rating Scale, as measured by two blinded neurologists at 3 months follow-up. While it is impossible to directly compare our studies, because the European trial did not report the number of patients with isolated cervical dystonia, different scales were utilized, and it involved a...
shorter follow-up, it is nonetheless encouraging that similar improvements in motor scores were obtained in both the trials.

There are several strengths to our study including its prospective multicentre design, the use of standardized videos and a validated scale for severity assessment by two neurologists unaware of the patients’ pre-operative or post-operative status. In addition, we did not dictate surgical technique or minimum severity of dystonia for study inclusion. Despite the original design as a small feasibility study, we achieved statistical significance for all outcomes.

While it would have been ideal to perform a double-blind study (Kupsch et al., 2006), we have been unable to blind our cervical dystonia patients involved in a comparative study on the effects of unilateral versus bilateral stimulation. Our patients know immediately which side is on or off because they experience a sensation of tingling, muscle relaxation or tightening. Only in patient 2, in whom stimulation was applied too dorsal in the globus pallidus initially, was a blinded N of one study inadvertently performed. Both the nurse and patient thought optimal stimulation was being applied. Instead the electrode poles activated were likely in the external segment of the globus pallidus. When the cathodal active electrode was switched to one in the posteroventral GPi, rapid clinical benefit was obtained.

Results of DBS for cervical dystonia are better than those obtained from other contemporary surgical interventions. The only procedure still in use is the selective peripheral denervation and myectomy of neck muscles (Albanese et al., 2006). This operation produces improvements of 20–30% (Ford et al., 1999; Munchau et al., 2001). While a denervating procedure may be more economical than bilateral DBS implants, it requires specialized expertise, extensive post-operative physiotherapy (Bertrand and Lenz, 1995) and may require re-operation for re-innervation of target muscles (Albanese et al., 2006).

We could not identify factors that would predict degree of improvement in cervical dystonia. Matching that reported in an open-label series (Hung et al., 2007), 6 of the 10 patients had approximately 50% or better improvement in cervical dystonia severity as measured by TWSTRS (median 63% improvement). Three patients had <30% improvement (median 23% improvement) and one patient fared worse after surgery (by ~33%). This individual may have deteriorated due to depression, although worsening of dystonia was also observed in the European randomized controlled trial (Kupsch et al., 2006). To determine potential reasons why this patient and the other three improved less than the others, we examined specific factors thought to influence outcome, such as DBS electrode placement, surgical technique, experience and type of dystonia. The patient whose dystonia severity was worse at 12 months follow-up had correct DBS placement on MR imaging (Fig. 4C) as judged by two neurosurgeons unaware of clinical outcome. In one case with 23% improvement, the DBS electrodes may have been too medial (patient 4). In the other two patients, DBS electrodes were judged adequately positioned. The absence of an obvious relationship between electrode positioning and degree of improvement has been observed by others (Hung et al., 2007). The four patients with <30% improvement in TWSTRS severity scores had surgery in four different centres, two of which used microelectrode brain mapping and two centres that did not. Similar to other reports (Hung et al., 2007), clinical features of the cervical dystonia such as the presence of tremor or tonic/phasic components were not predictive of outcome. Therefore while there was some variability in the magnitude of response to therapy, 90% of the patients improved and 60% improved by ~50% or greater on motor scores. These objective scores do not take into account functional improvements which were better assessed by the total TWSTRS scores. Interestingly, despite <30% motor improvement in 4 patients, they all reported improvements in pain, disability and quality of life. Generally, patient-reported secondary outcome measures were consistent with the decreases in the severity of dystonia.

Adverse events were similar to that reported by other groups, although we had fewer hardware-related problems and more declines identified on neuropsychological testing. Complications were those inherent to DBS surgery, including self-limited mild weakness and stimulation-induced swallowing/speech disturbance. There were no hardware-related complications, despite cervical dystonia being a known risk factor for lead fracture (Yianni et al., 2004). This was likely because we devised specific methods to reduce this complication (Kiss et al., 2004b). Other larger trials such as the one published by the European DBS for Dystonia Study group reported four infections, and two hardware problems in 40 patients (Kupsch et al., 2006). One delayed infection requiring electrode removal occurred in a series of 10 patients with cervical dystonia alone (Hung et al., 2007). Because our sample size was small and follow-up was only 1 year, we may have underestimated the surgical risks of GPi-DBS in this study.

Our trial did identify changes in neuropsychological assessments in four patients Supplementary Material Table 2. These involved mainly subtle changes (1 SD or less) in memory and verbal skills. However significant declines (>2 SD) were seen in one patient in phonemic verbal fluency, and in another patient on tests of verbal memory. While this testing was performed on all patients as part of their routine care, it was not standardized. In fact, three of the four patients who showed changes and the only two with significant declines were from one centre. Although the neuropsychological data are notable, the changes were not global, and most importantly, all of these patients returned to their previous work and lifestyle. Therefore the clinical relevance of these changes is uncertain. While this finding requires further investigation...
with uniform tests and normative data across centres, the changes are likely limited to specific cognitive domains. Two other studies examined neuropsychological outcomes in dystonia patients subjected to GPi-DBS. Halbig et al. (2005) found similar changes: while there were no changes in the overall scores, individual patients improved and declined on certain tests. Vidalhie et al. (2007) reported improvements in neuropsychological scores in 22 young patients (median age 30 years) with generalized dystonia. The European DBS for Dystonia Study group trial did not perform neuropsychology as part of its protocol, and the other case series only performed the testing in selected patients (Hung et al., 2007).

Conclusion

This pilot, prospective, single blind study demonstrated that bilateral stimulation of the posterior ventral internal pallidus resulted in a sustained decrease in the severity of cervical dystonia, including improvements in pain, disability and quality of life in adults with cervical dystonia.

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References

Appendix

Members of the Canadian Study Group were as follows:

Neurologists:
Vancouver: Joseph Tsui; Edmonton: Wayne Martin; Calgary: Scott Kraft, Ranjiit Ranawaya, Oksana Suchowersky; Winnipeg: Douglas Hobson; London: Mandar Jog.

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Programming:
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Neuropsychological evaluation:
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Swallowing evaluation:
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