Bilateral pallidal stimulation in cervical dystonia: blinded evidence of benefit beyond 5 years

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The local injection of botulinum toxin is accepted as the first-line treatment of primary cervical dystonia. This approach provides adequate symptomatic relief for most patients, but up to one-third will have an unsatisfactory response. Deep brain stimulation of the globus pallidus internus has been increasingly used in dystonic syndromes that are refractory to best pharmacological approaches. Although cervical dystonia is the most common idiopathic focal dystonia, evidence for long-term responsiveness to pallidal stimulation is limited. The primary objective of this study was to prospectively collect outcome data from baseline to last clinical follow-up on patients with idiopathic cervical dystonia treated with bilateral pallidal stimulation. Blinded video assessment of examinations performed preoperatively and at last video assessment were performed. Ten patients had complete prospective clinical follow-up. Baseline total Toronto Western Spasmodic Torticollis Rating Scale score (± standard deviation) was 54.5 ± 12.4 (range, 35.0–70.3). Comparison of the blinded severity sub-score on baseline video and at last video assessment at a mean of 7.7 years postoperatively demonstrated a mean improvement of 47.6% (P = 0.002) and strong inter-observer correlation between blinded raters (Spearman $r = 0.78$, 95% confidence interval 0.49–0.92, $P = 0.0001$). All 10 patients had 5 years of open prospective follow-up, documenting a 47.4 ± 26.4% ($P < 0.01$) mean improvement with respect to baseline. This was maintained at a mean of 7.8 years at last follow-up after surgery (range, 4.9–10.7 years) with a 54.4 ± 27.4% mean improvement ($P < 0.01$). Deep brain stimulation of the globus pallidus is an effective and long-lasting second-line treatment of cervical dystonia, with benefit in some of our patients extending to > 10 years. More data are needed to explain variations in individual responses and to guide individual programming parameters.

Keywords: deep brain stimulation; cervical dystonia; globus pallidus; parkinsonism
Abbreviation: TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale
Introduction

Although botulinum toxin can provide adequate symptom relief in most patients with idiopathic cervical dystonia, up to one-third will have an unsatisfactory response (Skogseid and Kerty, 2005). In these patients, either for reasons of complexity or resistance to the effects of botulinum toxin through neutralizing antibodies, alternative treatment strategies are required (Jankovic and Schwartz, 1999; Krauss et al., 2002a). Deep brain stimulation of the globus pallidus internus has replaced lesioning and selective peripheral denervation as the primary surgical option for treatment-refractory cervical dystonia, allowing bilateral intervention with an acceptable side-effect profile (Krauss et al., 1999; Loher et al., 2004; Krauss, 2007; Albanese et al., 2011). More evidence is available for globus pallidus internus deep brain stimulation in primary generalized dystonia (Krause et al., 2004; Vidailhet et al., 2007; Isaias et al., 2009), although a number of short-term studies (≤2 years mean follow-up) have also demonstrated clinically significant responses in primary cervical dystonia (Yianni et al., 2003; Bittar et al., 2005, Kiss et al., 2007, Jeong et al., 2009; Kim et al., 2012). Long-term outcomes in cervical dystonia, however, have been poorly documented. Published studies with more than a mean of 2 years of outcome data (Table 1) have demonstrated improvement between 49 and 83% on the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) at last follow-up (Hung et al., 2007; Loher et al., 2008; Skogseid et al., 2012; Yamada et al., 2012). Only one of these studies incorporated blinded severity assessments. In that study, 25% of the patients reported had open rating only, and clinical follow-up was as short as 12 months in some patients (Skogseid et al., 2012). The objectives of this study were to prospectively gather standardized physician and patient-reported outcome data from patients with idiopathic cervical dystonia treated with bilateral globus pallidus internus deep brain stimulation for at least 5 years and to perform rater-blinded comparison of preoperative and follow-up assessments.

Materials and methods

Patients

We included patients operated on consecutively for idiopathic cervical dystonia at the Toronto Western Hospital between August 2000 and January 2007, all of whom had at least 5 years of complete openly rated clinical follow-up data. For surgery to be considered, patients had to have (i) idiopathic cervical dystonia refractory to botulinum toxin or short-lived benefit after each treatment; and (ii) significant disability from involuntary movements, or pain or both. Patients with cervical dystonia referred for deep brain stimulation during this period were not considered for surgery if they had an active psychiatric illness or if they were felt to be medically unfit. Shorter, un-blinded follow-up data for some of these patients have been previously reported (Hung et al., 2007).

Surgical procedure

The targeting and operative procedures were described in a prior publication (Eltahawy et al., 2004). Preoperative MRI and intraoperative
Clinical assessments and postoperative programming

A movement disorders neurologist saw all patients preoperatively. Clinical assessment of the most prominent dystonic phenomenology was made to classify as either ‘tonic’ or ‘phasic’ depending on the presence of a fixed or more mobile dystonia, and the presence or absence of tremor was recorded. Video assessments were recorded preoperatively and postoperatively using a standardized protocol incorporating all elements of the TWSTRS motor severity sub-scale to allow rater-blinded assessment retrospectively (Hung et al., 2007; Moro et al., 2009). The initial programming of bilateral globus pallidus internus stimulation began after the micro-lesion effect wore off, leaving the patient at their preoperative baseline.

All postoperative assessments were performed in the stimulation-on condition in accordance with current recommendations, and our observation of rapid and unpleasant worsening of dystonia reported by some patients acutely after stimulation is turned off (Grips et al., 2007; Thobois et al., 2011). Patients were typically seen at 6 to 12 monthly intervals after initial stimulation settings were optimized. We report outcome data from those assessments taking place closest in time to 1, 2, 3 and 5 years from the date of surgery and from the last available follow-up visit. Contemporaneous patient-reported pain and disability TWSTRS sub-scores were also collected. Video assessments from the preoperative period (within 1 month of surgery) and the last clinical visit where a video was recorded were obtained. All dates were removed from the video clips, and no deep brain stimulation-related hardware or surgical wounds were visible. These videos were rated by two neurologists (R.W. and C.S.) experienced in the rating of cervical dystonia using the TWSTRS and who had not been involved in the management of these patients before surgery or during the programming of their stimulation.

Statistical analysis

The primary outcome measure was the blindly rated change in the mean TWSTRS motor severity sub-score between baseline and last available video assessments. Secondary outcome measures were the change in prospectively gathered open-rated total TWSTRS scores at 5 years and at last clinical follow-up as well as change in individual TWSTRS sub-scores (severity, pain and disability) for the same periods. All results were analysed on an ‘intention to treat’ basis, thus including patients who had leads removed or replaced to provide outcome data in a naturalistic fashion. Non-parametric repeated-measures ANOVA (Friedman’s test) was used to analyse the change in TWSTRS scores over the six studied time points: baseline, 1, 2, 3 and 5 years and last open assessment. Dunn’s multiple comparisons test was used to perform a post-test pair-wise comparison of each time-point to determine when statistically significant changes were taking place over time. Seven-year data were available for 7 of the 10 patients. For this subset, a Wilcoxon matched-pairs test was performed to compare 7-year outcome with preoperative assessments. Inter-rater reliability for the two blinded rating physicians observing pre- and last postoperative video assessments was determined using Spearman correlation. Mean TWSTRS severity sub-score values for both raters were taken when comparing pre- and postoperative blinded scores using the Wilcoxon matched-pairs test. P-values of < 0.05 were considered significant. Mean values are quoted to facilitate comparison with previously published data (Table 1).

Results

Patients and timing of assessments

Of 12 consecutively operated patients since August 2000 with at least 5 years of follow-up, 10 had complete, prospectively gathered outcome data. Two patients had incomplete follow-up with missing visits owing to geographical distance from our centre and were therefore excluded. Patient demographics, baseline clinical characteristics and individual stimulation parameters at last follow-up visit are provided in Table 2. Seven patients were female. Mean age at onset was 45.9 ± 11.8 years, and mean age (±SD) at surgery was 55.5 ± 12.8 years. Mean total TWSTRS score at baseline was 54.5 ± 12.4 (range, 35.0–70.3). The timing of routine postoperative clinical visits is provided in Table 3, with TWSTRS sub-scores and improvement from baseline at each time point. At the last clinic visit, the mean duration of open follow-up for all 10 patients was 7.8 ± 1.9 years. Preoperative and postoperative video assessments at last visit were available in 8 of the 10 patients, as Patient 3 had no baseline video and Patient 9 had no recent video assessment. The open-rated TWSTRS severity scores for these time-points were used in the analysis. The mean duration of video follow-up from baseline to last follow-up was 7.7 ± 1.9 years.

Blinded video follow-up

The blindly rated TWSTRS severity sub-score improvement at a mean of 7.7 years postoperatively was 47.6 ± 15.4%, significantly improved with respect to the preoperative video assessments (Fig. 1, P = 0.002). Video TWSTRS severity ratings showed strong inter-observer correlation (Spearman r = 0.78, 95% confidence interval 0.49–0.92, P = 0.0001). There was no significant difference between the rater-blinded video TWSTRS severity improvement after a mean of 7.7 years and the openly rated improvement after a mean of 7.8 years when seen at last routine follow-up as described below (P = 0.35).

Last prospective assessment

Last open clinical follow-up took place at a mean of 7.8 years (range, 4.9–10.7 years) after the initial surgery. Mean total TWSTRS improvement with respect to baseline was 54.5 ± 27.4% (P < 0.01); however, this was not significantly different from the improvement noted after 1 year (48.7 ± 17.8%) or any other time-point. Mean total TWSTRS score at last follow-up was 26.5 ± 17.5 (range, 1–61.8). Overall improvement in severity sub-score from baseline was 51.4 ± 27.7% (P < 0.05). Mean pain score was 7.7 ± 6.2 (range, 0–16.3) representing a mean improvement of 47.7 ± 35.0% (P < 0.05) with respect to
baseline scores, although only one of nine patients who had pain at baseline was pain-free and only three of the nine had >50% improvement in baseline pain scores.

Five-year postoperative outcome

After 5 years of chronic stimulation, the mean total TWSTRS score was 29.0 ± 14.4, which represented a 47.4 ± 26.4% improvement from baseline. Severity, pain and disability sub-scores improved by 52.6 ± 26.4%, 48.2 ± 26.0% and 47.6 ± 32.4%, respectively. Repeated measures ANOVA identified a significant difference for total TWSTRS score (F = 22.12, P < 0.0005) over the entire assessment period of one preoperative and five postoperative open assessments. Post-test analysis revealed that significant between-group changes were only seen when comparing the baseline total TWSTRS score with any postoperative time-point at 1, 3 or 5 years. No significant difference in total TWSTRS score was identified when comparing successive follow-up assessments (Table 3). At 5 years, there was a notable loss of the initial improvement in pain scores with respect to baseline at 2 and 3 years, but this was regained at last follow-up.

Seven-year postoperative outcomes

We report in addition, complete 7-year (6.8 ± 0.5 years) outcome data that were available for 7 of the 10 patients (Fig. 2). For these seven patients, mean total TWSTRS improvement from baseline was 58.3 ± 23.7% at 7 years with respect to baseline (P = 0.0156). Improvements in severity, pain and disability sub-scores at 7 years were 52.2 ± 17.3% (P = 0.02), 52.4 ± 39.8% (P = 0.03) and 70.1 ± 31.1% (P = 0.02), respectively. Six of these patients had completed >7 years of chronic stimulation at the time of last clinic follow-up (9.0 ± 1.2 years), and in this sub-set at 9 years, improvements in severity, pain and disability with respect to baseline were retained at 55.5 ± 23.7%, 63.5 ± 38.2% and 82.8 ± 24.0%, respectively.

Complications and side effects of stimulation

There were no acute perioperative complications. Any stimulation-related complications that did occur were late in the postoperative period. Two patients required a second surgery to have one lead removed due to infection that could not be adequately treated.
with intravenous antibiotics alone; one at 9 months (Patient 3) and the other at 62 months postoperatively (Patient 2). This allowed observation of the effect of unilateral stimulation (Fig. 3). Stimulation of the globus pallidus internus contralateral to the overactive sternocleidomastoid muscle provided 3 years of good clinical benefit before replacement in Patient 3. In Patient 2, stimulation ipsilateral to the overactive sternocleidomastoid muscle maintained a 54.7% total TWSTRS improvement after 2 years of unilateral stimulation. At last follow-up, 5 years after removal of the infected lead, this patient has retained most of this benefit with a 43.0% total TWSTRS improvement compared with baseline and has not required replacement of the removed lead.

Patient 8 had both leads repositioned within the globus pallidus internus after an initial 48% improvement at 1 year had diminished to 19% at 2 years. Most notable in the deterioration was a loss of the pain response seen after 1 year, with the pain sub-score returning to 12.5, despite an initial drop from 16.75 to 0 after 1 year of stimulation. It was determined that lead placement was suboptimal and a second surgery was performed. Both leads were replaced in a site immediately posterior to the original site of stimulation, which on postoperative MRI appeared to be localized better to the posterior portion of the globus pallidus internus. There was again improvement of 45% following the second surgery, with the pain sub-score dropping to 0 at the first assessment after the second surgery. At last follow-up (6.6 years after the first surgery), her total TWSTRS score of 62 was unchanged from baseline. However, this was despite a clinical impression of definite reduction in the prominent jerky dystonic movements observed in her preoperative video (see Supplementary Video).
Two patients with no clinical evidence of dystonia involving the upper limb complained of a gradual deterioration in handwriting and fine finger movements. Stimulation was programmed well below the threshold for pyramidal contractions. Subjective and qualitative assessment of handwriting at last assessment compared with baseline demonstrated clear micrographia (Fig. 4). Change of contact(s) stimulated or amplitude of stimulation did not improve this without losing the benefit on the symptoms of cervical dystonia. Low frequency stimulation was not attempted because it is our experience that it is less effective in cervical dystonia, and the disability was minimal in these patients. A third patient complained of deterioration in handwriting with no change to see on comparison of pre- and postoperative writing, but mild unilateral upper limb rigidity was found on examination. Two patients had clinical evidence of dystarthisia that was acute responsive to changes in stimulation parameters and was therefore felt to represent stimulation of cortico-bulbar fibres. This stimulation side-effect was also difficult to manage without loss of benefit.

**Stimulation settings and battery life**

Two patients had exclusively single channel (Soletra, Medtronic) pulse generators implanted, and the remaining eight had dual channel (Kineta, Medtronic) devices.

Programming was initiated a mean of 21.7 days (range, 6–39 days) after surgery. At last follow-up, 17 of 19 electrodes in the 10 patients were programmed with a monopolar setting (Table 2). The mean amplitude, frequency and pulse width of the 19 electrodes were 3.06 V, 157 Hz and 89 µs, respectively. Six single-channel batteries and 10 dual-channel batteries were replaced in 14 procedures. One patient (Patient 8) has had three internal pulse generator replacements. This patient has been treated with high frequency and high pulse width stimulation bilaterally, with double-monopolar stimulation on one side following a loss of the response to initial settings. Mean battery life of all 16 replaced batteries was 4.4 years (range, 1.7–6.3 years). Mean battery life was 2.9 years for those batteries set at higher pulse widths (>90 µs) compared with 5.0 years for those set at ≤90 µs. There was no significant difference between the mean lifespan of the six single-channel batteries replaced (4.7 years) and the 10 dual-channel batteries replaced (4.2 years).

**Discussion**

We provide both the longest open-rated follow-up of chronic bilateral globus pallidus internus stimulation in primary cervical dystonia, with outcome data up to 10 years in some patients. Importantly, we also provide rare rater-blinded follow-up of 5 years longer duration than the only previously reported blinded study (Skogseid et al., 2012). The most notable finding of this study is the persistence of significant symptomatic improvement after at least 5 years of bilateral globus pallidus internus stimulation. This was sustained after 7 years in 7 of 10 patients and beyond 10 years in two of the patients with longest follow-up. No significant differences in total TWSTRS score or severity sub-score were identified beyond the first year, confirming a sustained motor benefit over time.

As in previously reported series, our cohort demonstrated progressive improvement in motor severity over the first 2 years, although the majority of the response was clearly seen in the first 12 months. The response to pain behaved differently to the motor response. The postoperative change did not become significant with respect to baseline until the 2-year assessment. Greater variability before surgery may partly account for this. The pain response in a number of patients at last follow-up was also somewhat disappointing, despite a significant group change. Our understanding of the response of pain to globus pallidus internus deep brain stimulation is important when discussing potential outcomes with patients before surgery, many of whom will cite pain as a major factor in their overall disability (Chan et al., 1991). It is likely that pain has a multifactorial aetiology in some patients, with contributions from degenerative cervical spine disease, dystonic muscle spasm and an additional and poorly understood central component (Lobbezoo et al., 1996; Chawda et al., 2000). The late deterioration in pain control in some, despite sustained...
motor benefit, may represent progression of underlying degenerative spinal disease, although we have no cervical imaging evidence for this. Given our (unpublished) experience, and reports in the literature highlighting the co-existence of degenerative cervical spine changes in some patients with cervical dystonia, we now routinely perform cervical spine MRI preoperatively to help set expectations in relation to the pain response (Krauss et al., 2002a; Bronte-Stewart et al., 2011). Other authors have interpreted the dissociation between physician-rated motor scores and pain scores in terms of the functional anatomy of the globus pallidus internus (Kulisevsky et al., 2000; Cacciola et al., 2010). Perception of pain in cervical dystonia and the complex interaction between improved symptom control and patients’ self-evaluation of symptoms require further study (Lobbezoo et al., 1996; Hariz et al., 2011).

Of note, the patient who required bilateral electrode repositioning due to a loss of benefit had no net change in total TWSTRS score at last follow-up with respect to baseline. This was despite a clinical impression of definite improvement and a subjective rating of being ‘100% better’. At the last clinic assessment, sustained dystonic posturing remained, but the jerky, more mobile dystonic movements that were almost continuous at baseline were considerably reduced (see Supplementary Video). The TWSTRS is the only validated and most widely used clinical tool for the assessment of cervical dystonia (Consky et al., 1990). There are deficiencies that have been highlighted, including the absence of a tremor sub-score and a bias towards tonic as opposed to phasic movement (Comella et al., 1997; Thobois et al., 2011). This patient’s case is a good example of the difficulty in capturing change where phasic and tonic dystonic contraction co-exist. Future revisions of the TWSTRS should take this into account.

The need to remove one lead in two patients provided an opportunity to observe the effect of unilateral stimulation, improving symptoms with stimulation ipsilateral and contralateral to the involved sternocleidomastoid muscle in respective patients. The therapeutic potential of unilateral stimulation in cervical dystonia has previously been reported. The globus pallidus internus contralateral to the overactive sternocleidomastoid muscle has been targeted with good effect in some reported cases (Iskel et al., 1999; Foote et al., 2005; Torres et al., 2010), but there are also reports of good responses in cervical dystonia treated with stimulation ipsilateral to the overactive sternocleidomastoid muscle (Escamilla-Sevilla et al., 2002). This would be consistent with the finding of sternomastoid weakness ipsilateral to the side of the lesion in patients with a hemiplegia of vascular aetiology and the side of sodium amyloid b injection in subjects undergoing the Wada test (Mastaglia et al., 1986; DeToledo and Dow, 1998). The manner in which the sternocleidomastoid muscle is cortically innervated is unclear, although there is evidence to suggest that the sternocleidomastoid muscle has bilateral corticospinal innervation (Odergren et al., 1997). There are similarly conflicting reports of benefit in cervical dystonia following both ipsilateral and contralateral thalamic lesions (Laitinen, 1963; Cooper, 1964). Given the evidence of bilateral striatal dysfunction on imaging studies (Magyar-Lehman et al., 1994; Naumann et al., 1998), the uncertainty relating to the cortical innervation of the sternocleidomastoid muscle and the often complex and bilateral pattern of muscle involvement, bilateral intervention appears to be an appropriate choice in most patients (Krauss, 2003). The eventual loss of some benefit with unilateral stimulation in these two patients might suggest the effect of bilateral stimulation is additive rather than exclusively derived from one electrode. Further prospective and blinded studies are required to determine if there is actually dominance of one globus pallidus internus in the treatment of cervical dystonia.

The complaint and observation of micrographia or rigidity in 30% of the group warrants discussion. This is in keeping with reports that have attributed this phenomenon to stimulation of the more ventral ‘anti-kinetic’ region of the globus pallidus internus, also the region where active contacts can provide the greatest anti-dystonic benefit (Zauber et al., 2009; Blahak et al., 2011). Berman et al. (2009) found symptoms in keeping with lower limb bradykinesia in 9 of 11 patients treated with bilateral globus pallidus internus deep brain stimulation for cranio-cervical dystonia. This patient group, with dystonia limited to the head and neck region, is ideal for evaluating parkinsonism as a complication of pallidal deep brain stimulation, which may be more common than appreciated. If clinically significant parkinsonism is consistently found to complicate pallidal stimulation, long-term follow-up of bilateral subthalamic nucleus stimulation as an alternative target will be of interest and exploration of other targets such as the thalamus warranted (Krauss et al., 2002b; Chou et al., 2005; Ostrem et al., 2011).

Although some authors have studied the effects of alternative stimulation parameters acutely and up to 2 years postoperatively, the stability of response to the most commonly used parameters remains largely unknown (Moro et al., 2009; Kim et al., 2012). This study was not powered or designed to assess the relative efficacy of different parameters of stimulation. We can make the observation that an approach using low pulse widths and monopolar stimulation can achieve results in the range of those reported in studies favouring larger pulse widths and bipolar stimulation. Voltage and frequency have been shown to be more important to the acute motor response in cervical dystonia (Moro et al., 2009). This approach allows fewer internal pulse generator replacements and is an important consideration with respect to long-term costs.

Our study has several limitations that should be highlighted. Despite referrals coming from a large geographical area to a busy neurosurgical unit, our patient number is still relatively small. This reflects both the success of botulinum toxin in treating cervical dystonia and a probable bias towards more conservative management. Our patient number is insufficient to address other questions that need to be answered, such as the influence of chronic stimulation on the risk of spread of cervical dystonia and the true risk of parkinsonism. It is still, however, amongst the largest of studies of this kind in cervical dystonia. Also, effective binding of video taken in some cases over a 10-year period is technically difficult with changes in video quality and patient ageing. Videos were performed in the same clinic area, by the same staff members, and no surgical wounds were visible to minimize bias. Prospective blinded rating would be preferable, but it would have been difficult to find physicians unaware of the patients’ disposition on an ongoing basis.
In conclusion, globus pallidus internus deep brain stimulation should be considered a safe and effective first-line treatment for treatment refractory idiopathic cervical dystonia. It will be important to continue to follow larger cohorts of patients to better establish data on long-term efficacy beyond 10 years, to aid prediction of response in individual patients and to observe the evolution of extrapyramidal side-effects. Blinded physician rating should be the standard approach to evaluating outcomes. As evidence for sustained motor benefit following globus pallidus internus deep brain stimulation in cervical dystonia accumulates, our attention should also turn to how best we can assess those outcomes that are most meaningful to patients.

Supplementary material

Supplementary material is available at Brain online.

References


DeToledo JC, Dow R. Sternomastoid function during hemispheric suppression by amytal: insights into the inputs to the spinal nerve nucleus. Mov Disord 1998; 13: 809–12.


