

Chapter 50

Deep Brain Stimulation for Generalized Dystonia and Spasmodic Torticollis: An Examination of the Rate and Extent of Improvement

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Dystonia seems distinct from other tremulous disorders such as Parkinson's disease in that improvement after deep brain stimulation frequently appears in a delayed and progressive manner. The rate of this improvement and the point at which no further progress can be expected are presently unknown. Knowledge of these parameters is important in the provision of accurate and relevant prognostic information to these patients, as well as to their carers and physicians. We studied 12 consecutive patients with generalized dystonia ($n = 6$) and spasmodic torticollis ($n = 6$) who underwent bilateral globus pallidus internus (GPi) deep brain stimulation (DBS). Patients were followed for a minimum of 2 years after surgery. Both groups experienced a statistically significant improvement in their dystonia rating scores after surgery. At 2 years follow-up, the spasmodic torticollis group exhibited a 59% improvement in their total Toronto Western Spasmodic Torticollis rating scale (TWSTRS), and the generalized dystonia group attained a 46% improvement in their overall Burke, Fahn, and Marsden dystonia rating scale (BFMDRS) evaluation. Ninety-five percent of the final improvement was attained by 6.4 months in the generalized dystonia group and by 6.6 months in those with spasmodic torticollis. There was no significant improvement after 1 year after surgery. These findings further support to GPi DBS as an effective treatment for generalized dystonia and spasmodic torticollis and furnish important data as to the expected rate of improvement and the point at which no further gains can be reasonably anticipated.

Dystonia comprises a clinical syndrome in which sustained involuntary muscle contractions result in twisting and repetitive movements or abnormal postures (7). This group of movement disorders may be primary (idiopathic) or secondary and vary in their clinical expression, progression, and severity (2). Available treatment options include pharmacotherapy, botulinum toxin injections, and surgery. The growing adoption of deep brain stimulation for the treatment of intractable movement disorders has led to the emergence of pallidal stimulation as the surgical therapy of choice for many patients with dystonia (13). The efficacy of chronic GPi stimulation in the treatment of this group of abnormal involuntary movement disorders is supported by previous studies (12, 14, 15); however, the long-term outcome and pattern of clinical improvement is unclear. A detailed understanding of the outcome after this mode of treatment is imperative in facilitating the development of more realistic expectations of surgical therapy for dystonia, as well as the determination of optimal treatment parameters in each patient subgroup. Whereas DBS for Parkinson's disease yields an immediate clinical improvement (8), it seems that dystonic patients obtain a more gradual benefit after (14, 15) pallidal stimulation. Early data suggested that this improvement continued in a linear fashion for up to 2 years after treatment, but the exact pattern, duration, and extent of amelioration in this group of patients is unknown. In this prospective analysis of GPi stimulation for dystonia, we examine the course of postoperative clinical improvement.

METHODS

Patients

Twelve consecutive patients with medically refractory dystonia (six primary generalized dystonia (two DYT1 positive) and six spasmodic torticollis), treated with GPi DBS, and observed for at least 2 years were included in this study. The degree of dyskinesia was quantified using the BFMDRS (3) for generalized dystonia and the TWSTRS (4) for spasmodic torticollis. Assessments were performed preoperatively and at 3- to 6-month intervals after surgery.

Surgical Procedure

All patients underwent bilateral implantation of Medtronic 3387 DBS electrodes into the postero-ventral GPi under general anaesthesia. The preoperative magnetic resonance image was fused to the stereotactic computed tomographic brain using Image Fusion (Radionics, MA). The targets were localised using Stereoplan software (Radionics, MA). An immediate postoperative computed tomography scan, fused with the preoperative magnetic resonance image confirmed the electrode positions. Initial stimulation parameters were set in the following ranges, as tolerated by the individual patient: amplitude 2.5 to 7.0V, frequency 100 to 200Hz, and pulse width 90 to 210 μ s. These parameters were adjusted at each follow-up visit. The DBS electrodes used were those that did not produce any side effects on unipolar stimulation. Bipolar stimulator settings were used in all patients: the deepest available electrode was set to negative, the most superficial to positive, and any intervening electrodes remained neutral.

Analysis of Results

The results were analysed by applying the Wilcoxon signed rank test to compare rating scales within each group (before surgery and at the most recent follow-up visit). A statistical threshold of $P < 0.05$ was considered significant. The rating scores were averaged across each group of patients at the time of each clinical assessment. The regression of the average score was obtained from the mean values using exponential function $\text{Score} = y_0 + A \times \exp(R \times \text{Time})$. The variables y_0 , A , and R were estimated using OriginLab (version 7.0; OriginLab Corporation, Northampton, MA). The time taken to reach 95% of the total reduction in scores was determined from the regression curve.

RESULTS

Twelve patients (10 men and 2 women, mean age, 34.8 yr) underwent GPi DBS. Mean follow-up was 29.9 months (range, 24–48 mo). Postoperative computed tomographic brain, fused with T1W magnetic resonance image, confirmed placement of the electrodes in the postero-ventral GPi in all cases.

Mean pulse generator parameter settings at discharge and at most recent follow-up are displayed in Table 50.1. There was no statistically significant difference between the generalized dystonia and spasmodic torticollis groups. In both groups, there was an increase in amplitude and pulse width between discharge and latest follow-up.

The disability scores (before surgery and at 1 and 2 yr after surgery) for the subjects in both groups are summarized in Table 50.2. There was a statistically significant improvement in the generalized dystonia and spasmodic torticollis groups between the preoperative evaluation and evaluation at 1 year after surgery and between the preoperative and 2-year postoperative evaluations. A statistically significant difference was not demonstrated between 1 and 2 years after surgery, suggesting that the majority of benefit was derived in the first 12 months after surgery, and further

improvement after this point was minimal.

Statistically significant reductions in the mean severity of the dystonia, resultant disability, and total scores ($P < 0.03$ for each score) were observed in the generalized dystonia group at follow-up. All patients in this group obtained a demonstrable benefit, with the greatest improvement evident in the severity score component of the BFMDRS evaluation. At 2 years after surgery, the severity score had improved by 46% and the disability score by 39%.

The spasmodic torticollis group exhibited a greater mean percentage improvement and less inter-patient variability than the generalized dystonia group. Improvements in all aspects of the TWSTRS rating scale were observed ($P < 0.03$) at follow-up. Pain was the first symptom to be relieved in the majority of spasmodic torticollis patients. At 2 years after surgery, the severity score had improved by 58%, the disability score by 62%, and the pain score by 58%.

Whereas there was a demonstrable improvement at 1 and 2 years (compared with the preoperative evaluation) in both groups, there was no statistically significant difference between evaluations at 2 years compared with 1 year after surgery. A slight worsening in neurological status was observed at 2 years (compared with the scores at 1 yr after surgery), although this was not statistically significant.

Rate of Improvement

The time course of improvement in BFMDRS/TWSTRS scores for each group of patients is depicted in Figures 50.1 and 50.2. The total neurological rating scores for each group of patients improved gradually before reaching a plateau. The generalized dystonia group reached 95% of their total improvement at 6.4 months. Within the BFMDRS evaluation, the disability score improved at a slower rate (95% of total improvement attained at 9.7 mo) than the severity score (5.7 mo). The spasmodic torticollis group reached 95% of their maximum improvement by 6.6 months. The severity and disability components of the TWSTRS rating score improved at approximately the same rate (95% of total improvement at 7.3 and 7.4 mo, respectively); however, the pain subscale improved more rapidly, reaching 95% of its final improvement by 4.4 months.

Postoperative Medical Therapy

Ten patients were able to cease medical therapy for dystonia after surgery. Two patients continued taking oral pharmacotherapy, albeit at a considerably reduced dosage. One spasmodic torticollis patient required ongoing botulinum toxin therapy after surgery.

Adverse Events

Postoperative complications occurred in three patients. Electrode displacement and subsequent neurological deterioration occurred in one patient several months after surgery as a consequence of a playground accident. Replacement of the electrode was complicated by infection, which required the removal of all hardware. Further neurological deterioration ensued, and the development of spasmodic laryngeal dystonia required intensive care unit admission for intubation and ventilation. Resolution of the infective process permitted the successful replacement of both electrodes and implantable pulse generator. Two other patients experienced a similar acute rebound phenomenon, precipitated by a damaged lead connector in one patient and failure of the pulse generator battery in

the other. Both patients were treated with urgent replacement of the relevant hardware and demonstrated a rapid recovery. A fourth patient, with alcohol-responsive dystonic symptoms and significant improvement in neurological function with DBS, requested that the stimulators be removed in preference to reducing his alcohol consumption.

DISCUSSION

Relief from dystonia after thalamotomy and pallidotomy has been reported in previous studies (1, 5); however, the failure to achieve long-term relief in a significant proportion of patients, together with a higher complication rate in bilateral lesion procedures, has led to the emergence of DBS as the surgical procedure of choice in these patients.

DBS of the thalamus, zona incerta, and pallidum has been used for the treatment of dystonia. The pallidum has emerged as the target of choice (10, 11) on the basis of lesion results and that the dystonic dyskinesias seen in Parkinson's disease responded well to pallidotomy (9). Previous work by our group (14) demonstrated that GPi stimulation offers effective treatment for a wide range of dystonic conditions, excluding posttraumatic hemidystonia. Although DYT1-positive patients seem to derive the greatest benefit from surgery (6), chronic pallidal stimulation has also been of benefit to other patients with generalized and cervical dystonia (14, 15).

It was previously thought that dystonic patients derived neurological improvement at a linear rate after pallidal stimulation (13, 15). Our analysis of patients with a longer follow-up provides evidence that this pattern of improvement is exponential and plateaus midway through the first year. This knowledge is important in the provision of accurate prognostic information to patients and clinicians, in the monitoring of improvement of different patient subgroups and in the determination of optimal treatment parameters.

Adverse outcomes in this series are common and serious and may be subdivided into mechanical (DBS lead) complications, infection, and "status dystonicus." These complications highlight several points. First, DBS failure in dystonic patients is a medical emergency, and its recognition and prompt treatment is imperative. Second, the relatively high rate of mechanical complications suggests that a modification of the current electrode and lead fixation systems may be worthwhile. Third, unexpected battery failure represents a real hazard to these patients, and a more accurate and accessible means of establishing the amount of battery life remaining is important. Although we did not experience any clinically significant intracranial haemorrhages or postoperative neurological deficits in this series, such complications are well documented after stereotactic intracranial procedures. We attribute the absence of these complications to careful preoperative assessment of the patients' coagulation status and medications, meticulous intraoperative and postoperative blood pressure control, and few passes through the brain parenchyma.

In conclusion, GPi DBS for generalized dystonia and spasmodic torticollis is an effective means by which to achieve symptom amelioration and functional improvement. The improvement after surgery is not immediate, occurring in a gradual and exponential manner. Over 90% of the total expected improvement occurs within the first 6 months, and significant improvement after 12 months is infrequent.

TABLE 50.1. Mean pulse generator parameter settings at discharge and at most recent follow-up

Group	Parameters at discharge			Parameters at last follow-up		
	Amplitude (V)	Pulse width (is)	Frequency (Hz)	Amplitude (V)	Pulse width (is)	Frequency (Hz)
Generalized dystonia	3.3 ± 0.7	145.0 ± 51.7	125.8 ± 35.7	5.6 ± 0.7	225.0 ± 67.7	143.3 ± 24.3
Spasmodic torticollis	3.9 ± 0.7	157.5 ± 61.8	142.5 ± 51.4	5.8 ± 0.6	168.8 ± 66.4	143.8 ± 24.3

TABLE 50.2. Outcome after bilateral GPi DBS for generalized dystonia and spasmodic torticollis^a

	Preoperative (mean ± 1 SD)	1 yr after surgery (mean ± 1 SD)	2 yr after surgery (mean ± 1 SD)	Mean improvement 1 yr before surgery	Mean improvement 2 yr before surgery	Wilcoxon signed ranks test 1 yr before surgery	Wilcoxon signed ranks test 2 yr before surgery
BMFDRS							
(generalized dystonia)	103.8 ± 32.1	47.5 ± 30.5	55.8 ± 37.8	54.20%	46.20%	<i>P</i> < 0.03	<i>P</i> < 0.03
TWSTR							
(spasmodic torticollis)	57.8 ± 8.2	21.8 ± 8.7	23.7 ± 17.4	62.30%	59.00%	<i>P</i> < 0.03	<i>P</i> < 0.03

^aGPi, globus pallidus internus; DBS, deep brain stimulation; BMFDRS, Burke, Fahn, and Marsden dystonia rating scale; TWSTR, Toronto Western Spasmodic Torticollis rating scale.

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FIG. 50.1 Rate of improvement of BFMDRS severity, *A*, disability, *B*, and total, *C*, scores after GPi DBS for generalized dystonia (*vertical bars* represent the SE of the mean score).

FIG. 50.2 Rate of improvement of TWSTRS severity, *A*, disability, *B*, pain, *C*, and total, *D*, scores after GPi DBS for spasmodic torticollis.