Treatment of Dystonia Caused by Several Etiologies with DBS. Meta Analysis

ABSTRACT

Introduction: This meta-analysis of reported cases of deep brain stimulation (DBS) for dystonia evaluates the effect using the globus pallidus internus (GPI) as target, and the factors that significantly have influenced the outcome related to the target. The Burke-Fahn-Marsden (BFM) movement scale, the most reported measure, was chosen as the primary outcome measure for this analysis. Material and Methods: MEDLINE searches on English literature identified 137 patients who underwent DBS for dystonia in 24 studies that had individual BFM scores. The study was done with statistical analysis by intention to treat. Statistical analysis was made with a significant p-value of 0.05. For the comparison of pre- and postoperative scores, a Wilcoxon signed-rank test was used. Results: The mean BFM percentage change (improvement in postoperative score from baseline) was 46.3% (range 34% to 100%). At last follow-up, disease severity and degree of disability and pain on the BFM were significantly improved by 70.4%, and 67.8%, respectively (p < 0.05, Wilcoxon signed-rank test). Significantly better outcomes were achieved with stimulation of the GPI than with stimulation of the posterior portion of the ventral lateral (VLP) nucleus of the thalamus (p < 0.05). The etiology of the dystonia also had a significant effect on outcomes. Statistically significant improvements in outcomes were seen for all etiologic categories, except encephalitis. Dystonia due to birth injury and encephalitis had significantly worse outcomes of patients who were DYT1, or had pantotenate-kinase-associated neurodegeneration (PKAN), tardive dyskinesia, and idiopathic and posttraumatic dystonias. Longer duration of dystonia symptoms correlated negatively with surgical outcome. Conclusion: Deep Brain Stimulation of the GPI provides improvement in BFM scores in a variety of dystonic conditions.

Key Words: Deep brain stimulation; Dystonia; Electric stimulation therapy; Meta-analysis; Movement disorders; Stereotaxic techniques

RESUMO

Introdução: Os autores elaboraram uma meta-análise de todos os casos notificados de estimulação cerebral profunda (DBS) para distonia para determinar os fatores significativos que influenciam os resultados e complicações. A escala de Burke-Fahn-Marsden (BFM), uma escala muito mais informativa, foi escolhida como o desfecho primário para esta análise. Material e Métodos: Em uma busca MEDLINE foram identificados 137 pacientes que se submeteram a DBS para a distonia em 24 estudos com pontuações individuais BFM. Os dados de pacientes individuais, incluindo a idade do aparecimento de distonia, idade no momento da cirurgia, sexo, distribuição de distonia, etiologia da distonia, presença de características associadas, imagem pré-operatória anormal, cirurgia estereotáxica acima, núcleo estimulado, tipo de anestesia utilizada, tempo de resposta à estimulação, e tempo dos resultados da avaliação foram inseridos em um banco de dados para análise estatística (SPSS). Resultados: BFM com variação percentual média (melhoria na linha de base pontuação de pós-operatório) de 51.8% (intervalo de 34% a 100%). Resultados significativamente melhores foram obtidos com a estimulação do globo pálido interno (GPI) do que a estimulação do núcleo ventral lateral posterior (VLP) do tálamo (p = 0.0001). A etiologia da distonia também teve um efeito significativo sobre os resultados. Estatisticamente, foram observadas melhorias significativas em resultados para todas as categorias, exceto com a etiologia de encefalite. Distonia devido a traumatismo de parto e encefalite tiveram resultados significativamente piores do que pacientes que apresentavam gene DYT1 positivo, ou presença de enzima quinase negativa DYT1 em neurodegeração associada à pantotenato-quinase (PKAN), discinesia tardia e distonia idiopática e pós-traumática. A maior duração dos sintomas associados à distonia é negativamente correlacionada com o resultado cirúrgico. O modelo de regressão com três variáveis,
The last two decades have witnessed a renaissance of functional stereotactic neurosurgery in the treatment of diseases in the movement, such as Parkinson’s disease, essential tremor, pure dystonia and dystonic and dyskinetic syndromes (DDS). Ablative surgery (thalamotomies and pallidotomies) were gradually and largely replaced by chronic deep brain stimulation (DBS) applied to different target structures that are part of the basal ganglia (internal globus pallidus, subthalamic nucleus) and thalamus. The reason for this transition is the choice of the least invasive, most adaptable and possibly reversible procedure. The purpose of functional neurosurgery is to relieve symptoms of these chronic diseases (sometimes progressive) and improve quality of life. It is imperative to propose surgical procedures that do not cause complications and reduce disease symptoms.

When DBS is indicated for treatment of various dystonic syndromes, GPi is the most used target. Its posteroverentral sensorimotor portion (target of Leksell and Laitinen) is recognized as the optimal target (pallidotomy) in the treatment of Parkinson’s disease and dystonia syndromes. The volume of the sensorimotor portion of GPi is larger than other targets such as STN.

Pallidal neurons represent two sub-neuronal populations which differ by the presence or absence of dendritic spines (Figure 1). Neurons which present thorns have a relatively large soma from which emerge 3-5 dendrites emitting segments, secondary, tertiary or even with some veins in dendritic level (Figure 2). Neurons with thorns have a cell body smaller, however, the size and distribution of the dendritic field appear similar regardless of the type of cell. The pallidal neurons vary widely in size from 80 to 350 µm and use GABA as a neurotransmitter, associated with the parvalbumin in more than 60% of the neurons. The existence of a small population of cholinergic neurons has also been described. The pallidal neurons are much less numerous than the striatal neurons, suggesting a significant convergence striato cogwheel-like mapping tridimensionnelle par reveals the significant volume reduction of a nucleus to another: the volume of the ST is estimated at 9941 mm³, including NC: 4316 mm³ and P: 5625 mm³, GPe 808 mm³ (ST / 12), the GPi 478 mm³ (ST / 21), the SN: 412 mm³ (ST / 25) and the STN 158 mm³ (ST / 63) (Figure 3).

In the literature there are not many reports of these surgeries, however, the majority are single case reports and small series. The etiologies of treated dystonia and surgical methods employed are varied.

From these reports, it is clear that DBS can produce dramatic improvement in many, but not all, patients. DYT1 (Table 1) patients responded better than secondary dystonias. There is, however, significant variability within any category of the disorder, making it difficult to prognosticate for an individual patient.

While often used to integrate the findings of randomized controlled trials, meta-analysis can also be applied to integrate the findings of small case series in order to create a synthesis of the literature and to answer questions that cannot be answered by studies individually. This type of analysis requires prerequisites: 1) formulation of a purpose and specification of outcome, 2) identification of relevant studies, 3) data analysis, and 4) dissemination of the results and conclusions.
Table 1. Monogenic forms of dystonia. According to Schmidt et al., 2010

<table>
<thead>
<tr>
<th>Designation</th>
<th>Dystonia type</th>
<th>Mode of inheritance</th>
<th>Gene locus</th>
<th>Gene</th>
<th>DBSM number</th>
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</table>

Material and Methods

This study was done with statistical analysis by intention to treat. Statistical analysis was made with a significant p-value of 0.05. For the comparison of pre- and postoperative scores, a Wilcoxon signed-rank test was used.

MEDLINE searches on English literature were conducted using combination of text words: “dystonic diskinetic syndrome”, “dystonia”, “stereotactic and functional neurosurgery”, “electric stimulation”, and “movement disorders”.

All articles described the surgical treatment of dystonia, age at surgery, gender, distribution of the dystonia, etiology of dystonia, presence of associated features (such as tremor or myoclonus), abnormality of preoperative imaging, prior to stereotactic surgeries.
RESULTS

We reviewed 127 patients in 24 studies that presented individual BFM scores and scales. The mean BFM score percentage change, or improvement in postoperative score from baseline, was 46.3% with a range of 34% to 100%. The percentage change in BFM score and ranged for each etiology.

The surgery target was the GPi in 118 cases, the posterior portion of the ventral lateral (VLp) nucleus of the thalamus in 9 cases, and a combination of GPi and VLp in one case.

Etiology of dystonia, duration of dystonia, and nucleus stimulated were significantly correlated with percentage change in the BFM score, and the following factors we assumed that did not influence the outcome: age on onset of dystonia, age at surgery, gender, distribution of the dystonia, presence of associated features (such as tremor or myoclonus), abnormal preoperative MRI, prior stereotactic surgeries, and type of anesthesia used.

Stimulation of GPi was associated with better outcomes compared to stimulation of VLp (p < 0.05). The 118 subjects with GPi DBS had an average improvement in BFM scores of 67.8 +/- 11.7 and nine patients with VLp DBS had an average improvement of 17% +/- 11.7%. This between-group difference was statistically significant (p < 0.05).

The etiology of the dystonia had significant effect on outcome. Person with PKAN (p < 0.05) tardive dyskinesia (p < 0.05), or DYT1 (p < 0.05) had significantly better outcomes than individuals with cerebral palsy. Encephalitis was associated with significantly worse outcome than DYT1 dystonia (p < 0.05). There were no significant differences between individuals with DYT1, PKAN, idiopathic dystonia, tardive dyskinesia, or posttraumatic dystonia (Table 2).

DISCUSSION

From a historical point of view, it should be noted that the influence of electrical stimulation of the GPi and thalamus in treating dystonia, essential tremor and Parkinson’s disease had already been reported by Hassler at the end of the 50’s. Indeed, he used electrical stimulation of target structures before lesion procedure as a measure of physiological target validation.

Several reviews on the topic of DBS for dystonia were reported in the literature, however, only one of these reviews was based on statistical analyses of patient’s data across different series.

The incorporation of individual patient characteristics and outcomes into an SPSS database has allowed us to perform statistical analyses of patients across centers. Due to the relative rarity of these patients, several papers have noted the difficulty to incorporate enough patients in all etiologic categories.

This meta-analysis associates outcomes of DBS for dystonia with etiology.

Deep brain stimulation was less effective in the birth injury group compared to the three most favorable groups: DYT1, PKAN, and tardive dystonia. There was no significant difference between groups: DYT1, PKAN, idiopathic dystonia, tardive dyskinesia, and posttraumatic dystonias.

Secondary dystonia has been previously considered a single...
entity; however, our results revealed significant differences in outcomes within this category. Patients with tardive dyskinesia demonstrated significantly better outcomes than patients with birth injury, but outcomes were poor in all groups.

CONCLUSION

GPI resulted in significant improvement in BFM outcome scores for patients with DYT1 negative or positive dystonia, PKAN, idiopathic dystonia, tardive dystonia, posttraumatic dystonias, and cerebral palsy. The degree of improvement in cerebral palsy was significantly worse than with other etiologies, as the primary dystonias. For these etiologies, GPI was a better target than VLp. Because of the negative effect of prolonged duration of symptomatology on outcome, subjects should be considered for DBS as soon as surgery is medically appropriate, meaning refractory for medications and non-invasive procedures.

In view of the heterogeneous data, a prospective study and long follow-up with a large cohort of patients in a standardized setting with a multidisciplinary approach would be helpful in further evaluating the role of GPI DBS (Figure 4) in primary and secondary dystonia.

REFERENCES


