STN and GPi-Deep Brain Stimulation for Primary Cervical Dystonia

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ABSTRACT

Objective: To evaluate the safety and efficiency of deep brain stimulation (DBS) in the treatment of primary cervical dystonia (CD) and to compare the difference between the STN (subthalamic nucleus)-DBS and GPi (Globus Pallidus internus)-DBS.

Study Design: Experimental study.

Place and Duration of the Study: Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, China, from January 2012 to December 2021.

Methodology: This study analysed the effects of DBS on 34 patients with primary cervical dystonia (CD) based on the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS). It included 15 STN-DBS and 19 GPi-DBS cases, with TWSTRS scores collected at baseline and the final follow-up. Stimulation parameters and adverse events were also recorded.

Results: The mean follow-up time was 42.77 ± 27.46 months. A significant improvement in TWSTRS total scores was observed in all patients ($p < 0.001$), with no significant difference between STN-DBS and GPi-DBS groups ($p = 0.481$). The amplitude of stimulation in the GPi group was found to be higher than that in the STN group ($p < 0.001$). Adverse events included one case of electrode breakage in the STN-DBS group, mild dyskinesias in 14 patients (twelve from the STN-DBS group and two from the GPi-DBS group), and other stimulation-related complications in four patients (one from the STN-DBS group and three from the GPi-DBS group). All stimulation-related complications were manageable with parameter adjustments.

Conclusion: DBS can significantly improve the symptoms of primary CD patients, with no significant difference in outcomes between STN-DBS and GPi-DBS. It has a good long-term therapeutic effect and surgical safety.

Key Words: *Cervical dystonia, Deep brain stimulation, Globus pallidus internus, Subthalamic nucleus.*

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INTRODUCTION

Cervical dystonia (CD) is the most common form of focal dystonia, characterised by abnormal and repetitive movements or positions of the neck muscles, patients often experience pain as well.[1]

Current treatments for CD, primarily encompass medicine therapies, such as botulinum toxin injections and oral medications. Surgical interventions include selective peripheral nerve sectioning and the modified Foerster-Dandy operation. Medications have limited effects in improving the symptoms of CD. Local injection of botulinum toxin also faces the problem of diminishing efficacy and insufficient results.[2]

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Although selective peripheral nerve sectioning and the modified Foerster-Dandy operation have good short-term effects, they involve significant surgical trauma and have a high recurrence rate.[3] Since the pioneering use of Globus Pallidus Internus-deep brain stimulation (GPi-DBS) for CD treatment by Krauss *et al*.,[4] followed by the introduction of STN-DBS by Chou *et al*.,[5] DBS has gained wider acceptance across numerous medical centres. DBS has become an increasingly effective therapeutic option for CD, with the GPi and the subthalamic nucleus (STN) serving as common stimulation targets. However, the application of DBS in CD treatment still lacks a comprehensive summary of large case series, especially in terms of comparing the efficacy and complications of GPi-DBS and STN-DBS.

This study aimed to evaluate the efficacy and safety of DBS for primary CD and to explore the differences between the two commonly used stimulation targets, the GPi and the STN.

METHODOLOGY

This study included patients who underwent DBS surgery for the treatment of primary CD at Beijing Tiantan Hospital, from January 2012 to December 2021. Patient data were extracted from an electronic database.

Eligibility for the study was determined by a confirmed diagnosis of primary CD by two movement disorder specialists. Participants received bilateral DBS targeting the STN or the GPi. The study included patients aged 16 to 80 years. Exclusions were applied to the patients with other types of segmental or generalised dystonia. Those with significant intracranial structural changes or other neurological disorders detected by MRI were also excluded.

DBS surgery began with the implantation of electrodes under local anaesthesia. Thereafter, electrodes were connected to an external temporary stimulator for three to seven days of temporary testing to assess the efficacy and adverse reactions. Upon achieving satisfactory results, patients underwent the second phase, which involved the implantation of a permanent stimulator. Approximately one month after surgery, the formal programming process began. The parameters were adjusted based on the patients' symptoms and response. The Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) was employed to assess patients' condition preoperatively and at the final follow-up.

The SPSS version 27.0 software (IBM, NY, USA) was used for data analysis. The normality of variables was assessed by Kolmogorov-Smirnov test. Normally distributed continuous variables were presented as mean ± standard deviation (x ± s) and compared by the t-test. The categorical indicators were described as the number of cases of each type and compared by Fisher's exact test. Non-normally distributed data were presented as M (Q1, Q3) and were compared by Mann-Whitney U test. A value of $p < 0.05$ was considered statistically significant.

RESULTS

This study enrolled 34 patients diagnosed with primary CD who received GPi-DBS (n = 19) or STN-DBS (n = 15) implantation. In the preoperative assessment, a significant difference was observed in gender and age at the time of surgery between the two targets (p = 0.007 and 0.008, respectively). In whole datasets, patients with CD had a significant improvement in total TWSTRS score ($p < 0.001$), severity score ($p < 0.001$), disability score ($p < 0.001$), and pain scores ($p < 0.001$). Thirty cases responded to DBS according to the TWSTRS total scores (defined as ≥25% improvement), while 4 cases did not respond (defined as <25% improvement) at the 42.77 ± 27.46 months follow-ups. Both targets showed improvement in TWSTRS total scores (GPi: $p < 0.001$, STN: $p < 0.001$), severity scores (GPi: $p < 0.001$, STN: $p < 0.001$), disability scores (GPi: $p < 0.001$, STN: $p < 0.001$), and pain scores (GPi: p = 0.001, STN: p = 0.007) at follow-ups. No statistical difference was observed between the two targets in improving total TWSTRS scores (p = 0.481), severity scores (p = 0.541), disability scores (p = 0.441), and pain scores (p= 0.914). In addition, the GPi-DBS group showed significantly higher voltages than the STN-DBS group ($p < 0.001$, Figure 1). Detailed information is shown in Table I.

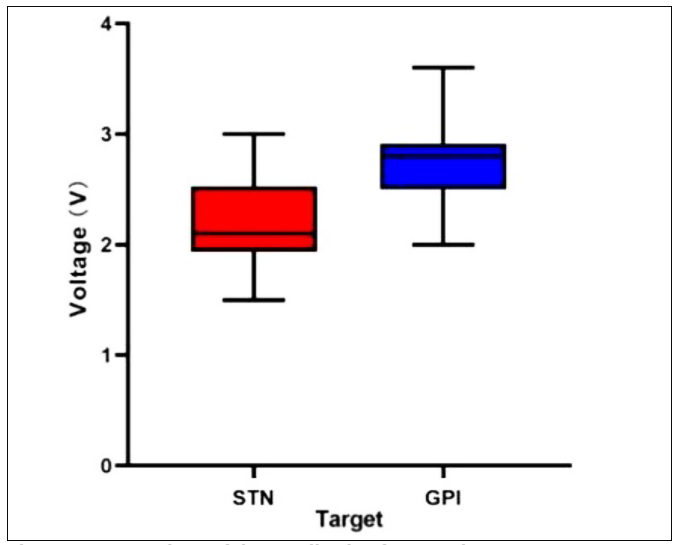

Figure 1: Comparison of the amplitude of STN and GPI.

Table I: Clinical and demographical features of CD patients with GPi- or STN-DBS at preoperative and postoperative assessments.

Characteristics	Total (n = 34)		GPi-DBS (n = 19)		STN-DBS (n = 15)		p-value
Preoperative assessment							
Gender (male:female)	18:16		6:13		12:3		0.007
Age at surgery (year)	48.18 ± 12.46		43.26 ± 12.31		54.40 ± 9.85		0.008
TWSTRS total	46.63 ± 12.99		45.28 ± 13.8		48.35 ± 12.14		0.502
TWSTRS severity	21.94 ± 4.58		20.58 ± 4.3		23.67 ± 4.47		0.049
TWSTRS disability	17.53 ± 6.01		17.37 ± 6.29		17.73 ± 6.02		0.865
TWSTRS pain	8 (0, 12.5)		7.75 (0, 13.3)		8 (0, 12.3)		0.944
Preoperative assessment		**p-value**		**p-value**		**p-value**	
Follow-up (mo)	42.77 ± 27.46		46 ± 20.43		38.67 ± 34.76		0.477
Pulse width (μs)	60 (60,70)		60 (60, 80)		60 (60, 70)		0.629
Frequency (Hz)	140 (130, 144)		140 (130, 146)		140(130, 140)		0.730
Voltage (V)	2.6 (2.1, 2.9)		2.8 (2.5, 2.9)		2.1 (1.9, 2.5)		<0.001
Surgical response (Yes/No)	30: 4		16: 3		14: 1		0.613
TWSTRS total	16.44 ± 13.56		16.95 ± 13.44		15.8 ± 14.16		0.811
Improvement rate	0.648 ± 0.272	<0.001	0.623 ± 0.304	<0.001	0.691 ± 0.243	<0.001	0.481
TWSTRS severity	8.68 ± 6.41		8.58 ± 6.34		8.80 ± 6.72		0.922
Improvement rate	0.596 ± 0.299	<0.001	0.571 ± 0.342	<0.001	0.634 ± 0.245	<0.001	0.541
TWSTRS disability	7.27 ± 6.34		7.84 ± 6.09		6.53 ± 6.89		0.561
Improvement rate	0.595 ± 0.334	<0.001	0.557 ± 0.355	<0.001	0.658 ± 0.326	<0.001	0.441
TWSTRS pain	0 (0, 0)		0(0, 0)		0 (0 ,0)		0.638
Improvement rate	0.888 ± 0.256	<0.001	0.892 ± 0.221	0.001	0.884 ± 0.321	0.007	0.914

Improvement rate = (preoperative score - postoperative score) / preoperative score × 100%.

Furthermore, aside from one case of electrode breakage in a patient who underwent STN-DBS during the follow-up period, no patients experienced adverse events (AEs) related to the surgical procedure or the device itself. Among the stimulation-related AEs, a total of fourteen patients—twelve from the STN-DBS group and two from the GPi-DBS group—encountered mild dyskinesias, which were successfully resolved after the adjustment of stimulation parameters. One patient from the GPi-DBS group presented with neck weakness, pain, dysarthria, and dysphagia; these symptoms experienced partial relief following parameter adjustments. A patient who received STN-DBS developed speech difficulties and ocular discomfort more than a year after the surgery; one GPi-DBS patient experienced mouth twitching, while another had facial tics. The reduction of stimulation parameters led to an improvement in these symptoms. All stimulation-related AEs were transient, with symptoms either completely disappearing or significantly reducing after the programming adjustments were made.

DISCUSSION

In recent years, DBS surgery for the treatment of CD has gained increasing attention; however, the number of participants in related studies has remained modest.[6-10] This study contributed to the field with a substantial single-centre sample size, comprising 34 patients with an extended follow-up period (42.77 ± 27.46 months). The near 1:1 ratio of STN-DBS (15 cases) to GPi-DBS (19 cases) provides a balanced perspective, enhancing the reliability of the statistical comparisons and minimising bias when assessing the relative merits of each DBS approach.

The findings indicate an improvement rate of 64.8 ± 27.2% in TWSTRS total scores for the 34 patients. This is in line with pooled meta-analyses,[10] which aggregated data from 39 papers to report on 208 patients, revealing a 58.8% improvement in the TWSTRS scores after an average follow-up of 23.3 months post-DBS. Another meta-analysis corroborated these findings, with significant symptom improvement and a mean reduction of 56.6% in TWSTRS scores among 86 CD patients treated with either STN-DBS or GPi-DBS.[9] The present study results further align with several studies,[11-13] that have documented symptom-improvement rates ranging from 54 to 76% in CD patients treated with DBS. Moreover, in the present study, among the 34 patients, 30 cases responded to DBS according to the TWSTRS total scores, which the authors defined as an improvement of at least 25%. This response maintained long-term stability. Notably, patients with the longest follow-up period of 10 years continued to exhibit substantial improvements.

Four patients, with TWSTRS improvement rates of 25% or less, included three who received GPi-DBS and one who underwent STN-DBS. Their ages were 50, 53, 65, and 68 years, respectively. Several studies have indicated that while CD typically develops in adults, younger patients may derive greater benefits from DBS therapy, primarily due to their superior neuroplasticity.[14] The outcomes for these four patients may be attributed to factors such as their older age, irregular follow-ups, and a lack of strict adherence to the post-treatment regimen.

STN and GPi have their own advantages and disadvantages as optional targets for CD. GPi-DBS has been used in CD earlier and it is still predominantly used.[9] Some studies have analysed that STN is slightly better than Gpi, and the difference between them has no statistical significance, but since the number of STN-DBS studies that can be included is much smaller than GPi-DBS studies, the bias that exists may affect the reliability of the results.[10,15] Therefore, the preference for GPi or STN is inconclusive. In the present study, there were no significant outcome differences between GPi-DBS and STN-DBS, consistent with previous research. Some studies have found that STN as a target for treating CD has advantages such as lower power consumption, simpler programming, and faster short-term effects compared to GPi.[9,10,16] In this study, the postoperative programming voltage for the GPi target was significantly higher compared to the STN target.

Disabling complications resulting from DBS for movement disorders are usually due to intraoperative injury to important areas of blood vessels, such as haemorrhage or infarction in the basal nucleus region.[17,18] No intraoperative bleeding, postoperative intracranial bleeding, infarction, or allergic reactions were observed in this study.

Regarding stimulation-related complications, GPi-DBS may cause gait disturbances and bradykinesia, which cannot be attributed to the spread of electrical stimulation to surrounding tissues and cannot be completely alleviated by adjusting the parameters.[19] Currently, no such issues have been observed with STN-DBS, although patients treated with STN-DBS are more prone to develop stimulation-related adverse effects such as dyskinesia, allodynia, dysgraphia, sensory impairment, and cognitive decline, which can generally be improved by lowering the parameters.[9,10] They are probably due to the small size of the STN, the periphery of STN is adjacent to numerous deep brain nuclei and nerve bundles; the STN is topographically structured internally, with a certain degree of overlap between subfunctional regions.[20] This means that stimulation currents are more likely to affect internal non-sensory motor areas and external peripheral structures. In this study, no gait disturbances or bradykinesia related to GPi-DBS were observed. Conversely, twelve patients who underwent STN-DBS reported dyskinesias, and this issue was also noted in two GPi-DBS patients. These motor symptoms were successfully resolved by adjusting the stimulation parameters, aligning with the outcomes reported in previous studies.

CONCLUSION

This study provides substantial evidence supporting the safety and efficacy of DBS in the treatment of primary CD.

The present study's findings demonstrate that DBS can lead to a substantial improvement in symptoms. Importantly, the authors found no significant difference in outcomes between the STN-DBS and GPi-DBS groups, suggesting that both targets are viable options for CD treatment.

ETHICAL APPROVAL:
The study was granted approval by the Ethics Committee of Beijing Tiantan Hospital, Beijing, China.

PATIENTS' CONSENT:
Informed consent was obtained from the patients.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
TW: Conception, acquisition of data, drafting of the work, and proofreading.
ZG, FS: Acquisition, analysis of data, and proofreading.
MF, YA: Conception and proofreading.
ZJ: Conception, acquisition, analysis and interpretation of data, and proofreading.
All authors approved the final version of the manuscript to be published.

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