



Dual Pallidal and Thalamic Deep Brain Stimulation for Complex Ipsilateral Dystonia

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Purpose: Globus pallidus pars interna (GPi) has become an established target for deep brain stimulation (DBS) in dystonia. Previous studies suggest that targeting the ventralis oralis (Vo) complex nucleus improves dystonic tremor or even focal dystonia. Research has also demonstrated that multi-target DBS shows some benefits over single target DBS. In this study, we reviewed patients who had undergone unilateral DBS targeting the GPi and Vo.

Materials and Methods: Five patients diagnosed with medically refractory upper extremity dystonia (focal or segmental) underwent DBS. Two DBS electrodes each were inserted unilaterally targeting the ipsilateral GPi and Vo. Clinical outcomes were evaluated using the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) and Disability Rating Scale.

Results: BFMDRS scores decreased by 55% at 1-month, 56% at 3-month, 59% at 6-month, and 64% at 12-month follow up. Disability Rating Scale scores decreased 41% at 1-month, 47% at 3-month, 50% at 6-month, and 60% at 12-month follow up. At 1 month after surgery, stimulating both targets improved clinical scores better than targeting GPi or Vo alone.

Conclusion: Unilateral thalamic and pallidal dual electrode DBS may be as effective or even superior to DBS of a single target for dystonia. Although the number of patients was small, our results reflected favorable clinical outcomes.

Key Words: Dystonia, deep brain stimulation, ventralis oralis, globus pallidus, multi target dbs

INTRODUCTION

Dystonia is a movement disorder presenting as sustained or intermittent involuntary muscle contractions.¹ Dystonia can be classified as focal, segmental, and generalized depending on the affected body area. Focal dystonia affects one region of the body, segmental dystonia affects adjacent regions, and general dystonia affects multiple areas.² Initial dystonia can be focal in nature but spread to other body parts and become generalized.¹ Several studies have investigated the genetic

causes of dystonia, but still many cases are idiopathic.³ In the past the pathophysiology of dystonia was thought to be the result of basal ganglia lesions; however, thanks to the development of many imaging and diagnostic techniques, recent studies suggest the disorder stems from dysfunction in the basal ganglia-cerebello-thalamo-cortical circuit.⁴

There are many pharmacologic treatments for dystonia, but for medically refractory dystonia, deep brain stimulation (DBS) is the treatment of choice.^{1,5} Several randomized control studies have proved the efficacy of globus pallidus pars interna (GPi) DBS in dystonia.⁵⁻⁸ The posteroventral lateral GPi has become the most established target for DBS in dystonia.⁵ However, some adverse effects have been found in patients with DBS. Problems with speech and swallowing have been recorded in some patients, and worsening of handwriting and stimulation-induced parkinsonism (bradykinesia or gait problems) have been reported in others.⁹⁻¹² Therefore, alternative targets, such as the subthalamic nucleus or ventrolateral thalamus, are being considered in light of their observed involvement in motor function control.¹³⁻¹⁶ Some previous studies suggest that targeting the ventralis oralis (Vo) complex nucleus improves dyston-

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ic tremor or even focal dystonia, such as writer's clamp.¹⁷⁻²¹ With this rationale, targeting multiple targets might improve dystonia better. In a study combining GPi and ventralis intermedius (Vim) as targets for DBS, significant improvements in myoclonus dystonia were recorded.²² However, only few studies have researched targeting both the GPi and Vo.²³ Here, in this study, we aimed to retrospectively review patients who underwent unilateral DBS of both the GPi and Vo for dystonia symptoms, including trunk and focal symptoms.

MATERIALS AND METHODS

Patient assessment

From June 2014 to March 2020, five patients diagnosed with medically refractory upper extremity dystonia (focal or segmental) underwent DBS at Severance Hospital, Yonsei University College of Medicine. The patients were diagnosed by an experienced neurologist or neurosurgeon. The operation was performed by an experienced and skilled senior professor with

assistance from a clinical fellow. Two DBS electrodes were inserted unilaterally targeting the ipsilateral GPi and Vo (Fig. 1).

Patients included in this study had symptoms of complex hemidystonia with more serious involvement in the upper extremities. Dystonic patients were fairly disabled upon assessment of dystonia severity and disability level and had failed pharmacologic treatment. Patients were not offered surgery unless their symptoms were disabling and unless they had failed to respond to standard pharmacologic therapies (baclofen, benzodiazepines, anticholinergics, etc.). Magnetic resonance imaging (MRI) scans of the brain were obtained to rule out other brain lesions. Genetic testing was performed to confirm potential genetic causes of dystonia. Patients with poor general condition or other major medical diseases, such as cardiovascular problems or psychiatric disorders, were excluded.

Clinical outcomes were evaluated by an experienced examiner using the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) and the Disability Rating Scale. Each were measured pre-operatively and at 1-month, 3-month, 6-month, 1-year post-operation. DBS stimulation targeted the GPi when

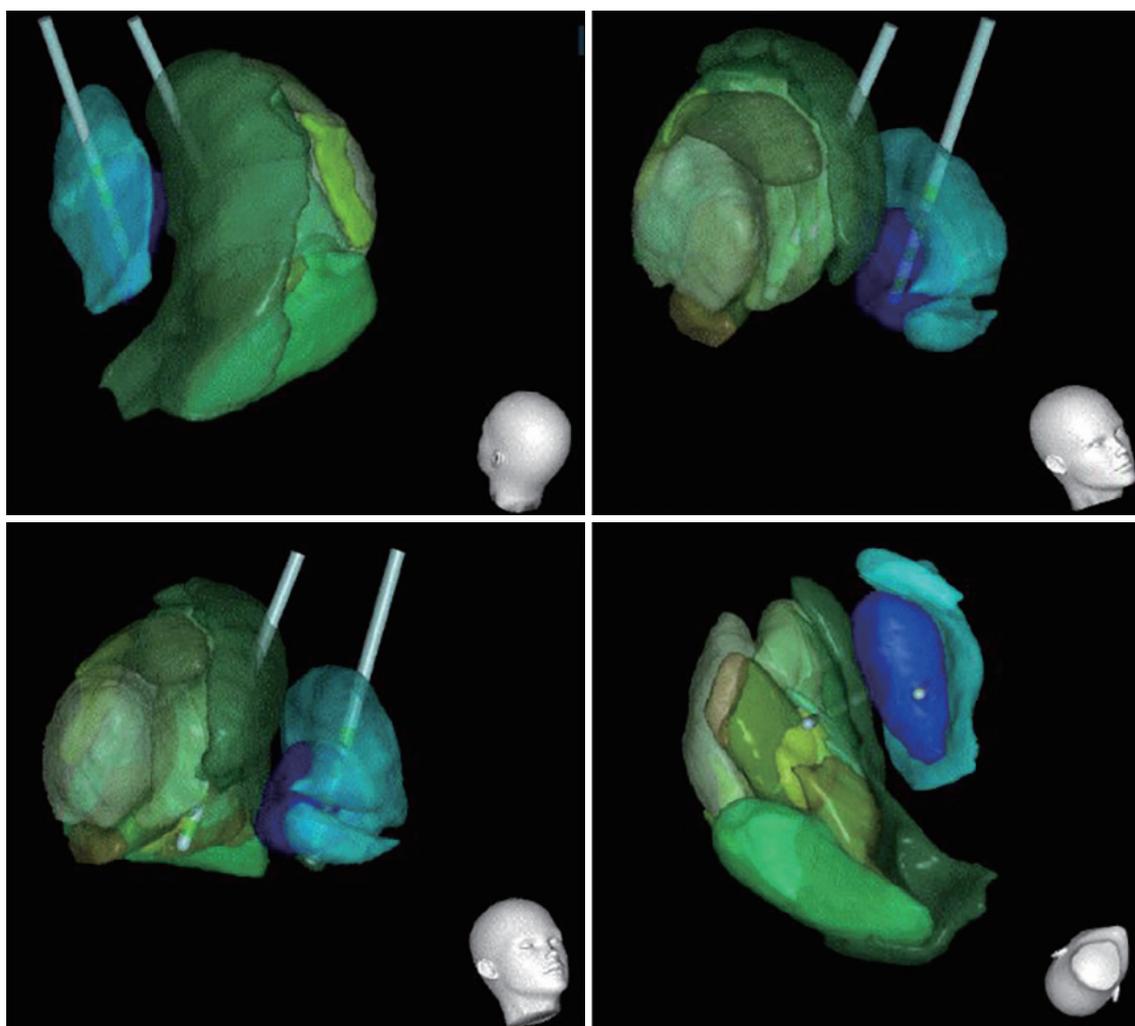


Fig. 1. Three-dimensional reconstruction image of inserted electrodes (blue, globus pallidus pars interna; sky blue, globus pallidus pars externa; green, thalamus). Image reconstructed by Medtronic SureTune.

the patient was discharged from the hospital, since GPi stimulation has late gradual effects. DBS stimulation was programmed by an experienced neurosurgeon or neurologist. At follow-up visits, stimulation of each of the GPi or Vo alone was performed to compare clinical outcome scores for each target. After evaluation of each target, stimulation on both target electrodes were turned on. The Mann-Whitney U test were applied to compare BFMDRS and disability scores before and 1 year after surgery and also between single target and dual targets. All statistical analyses were performed using IBM SPSS software, version 25 (IBM Corp., Armonk, NY, USA).

Surgical procedures

A Leksell stereotactic frame (Elekta Instruments, Atlanta, GA, USA) was fixed to the skull of the patient under local anesthesia. MRI scans were obtained after fixation of the stereotactic frame. The stereotactic target was measured using SurgiPlan (Elekta Instruments) and SureTune (Medtronic, Minneapolis, MN, USA) software. Generally, the GPi was targeted 4 mm inferior, 21 mm lateral, and 2 mm anterior to the mid-commissural point. The Vo was targeted 1 mm dorsal, 14 mm lateral, and 2 mm posterior to the mid-commissural point. Targets were modified according to the length of the anterior commissure-posterior commissure line, and the width of the ventricle based on the Schaltenbrand-Wahren atlas. The operation was performed awake with local anesthesia. Microelectrode recording and electrical stimulation were employed to identi-

fy the ventral thalamus insertion area, and C-arm fluoroscopy was used to confirm the tip of the electrode. During the operation, patients were asked to report symptoms and side effects after micro- and macro-stimulation with electrodes. Micro-stimulation was performed at a target -4 mm, -2 mm, and 0 mm, with a stimulation pulse width of 90 uS and a frequency of 130 Hz. In each target, the stimulation was increased 4 V until there were side effects. If there were side effects, the symptoms were recorded. Macro-stimulation was performed in the same manner at contact 0 and contact 2 of the electrode. A quadripolar DBS electrode (model 3387; Medtronic, Inc.) was inserted to either targets. The distal contact (contact 0) of the quadripolar electrode was placed into the target. After confirming the trajectory with merging post-operative computed tomography (CT) images and pre-operative planned pathway using the SurgiPlan software (Elekta®, Stockholm, Sweden), implantation of one Activa RC (or two Activa SC) pulse generator was performed under general anesthesia in the chest area (Figs. 2 and 3).

RESULTS

In total, five patients underwent dual pallidal and thalamic DBS in ipsilateral GPi and Vo according to the patients’ side of symptoms. Target error was less than 1 mm in all patients by checking with the SurgiPlan software (Fig. 2). Three patients

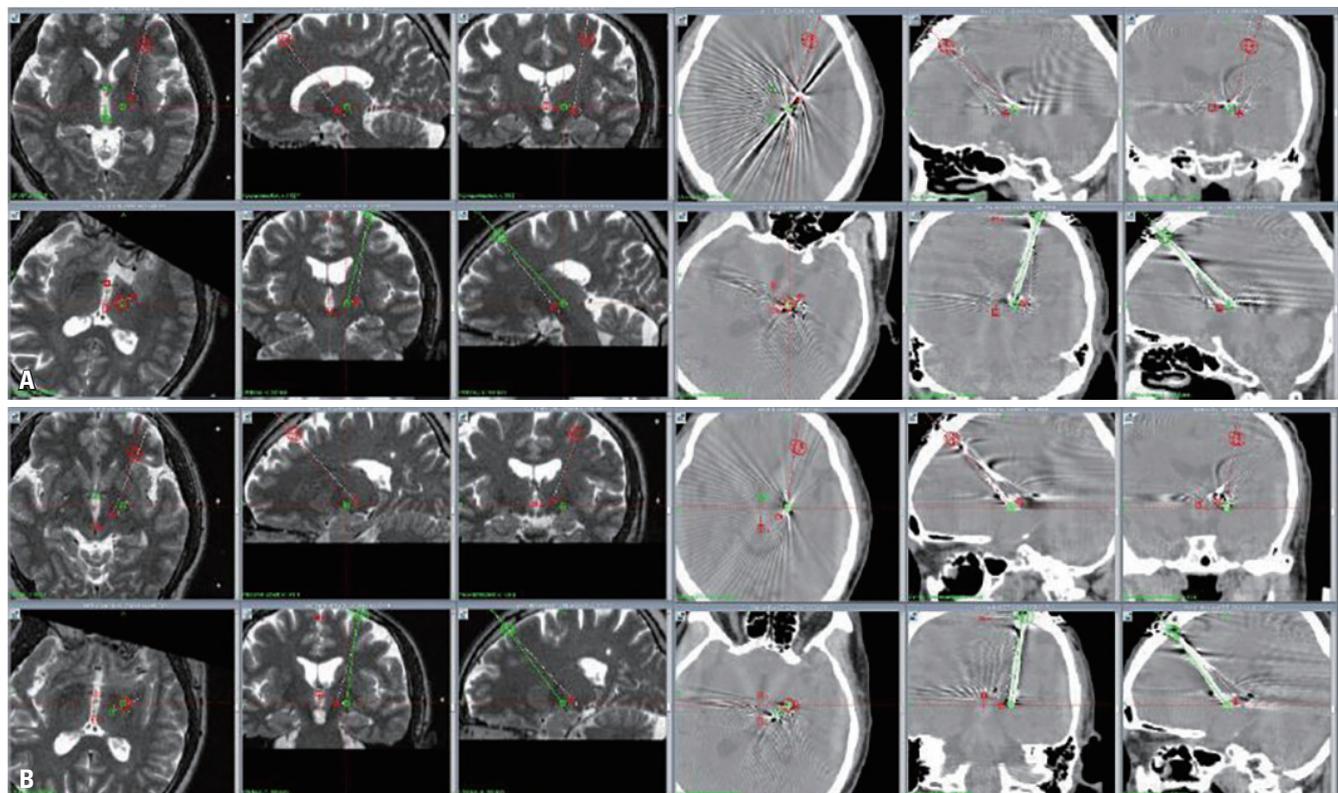


Fig. 2. Pre-op trajectory planning and post-op CT trajectory confirmation of (A) ventralis oralis and (B) globus pallidus pars interna using SurgiPlan software.

were targeted at the left side, and two patients were targeted at the right side. All patients were male, with ages ranging from 32 to 53 years. Average symptom period from age of onset to age of surgery was 28.4 years. Average pre-operative BFMDRS and Disability Rating Scale scores were 17.4 and 6.4, respectively. Mean follow-up period was 3.7 years (Table 1). Stimula-

tion parameters were programmed according to observed clinical benefit and adverse effects (Table 2). There were no serious adverse effects in any patient after DBS. One patient kept stimulation in the Vo only, since the patient was significantly improved with no remnant symptoms: this patient was excluded from the statistical analysis. BFMDRS and Disability Rating

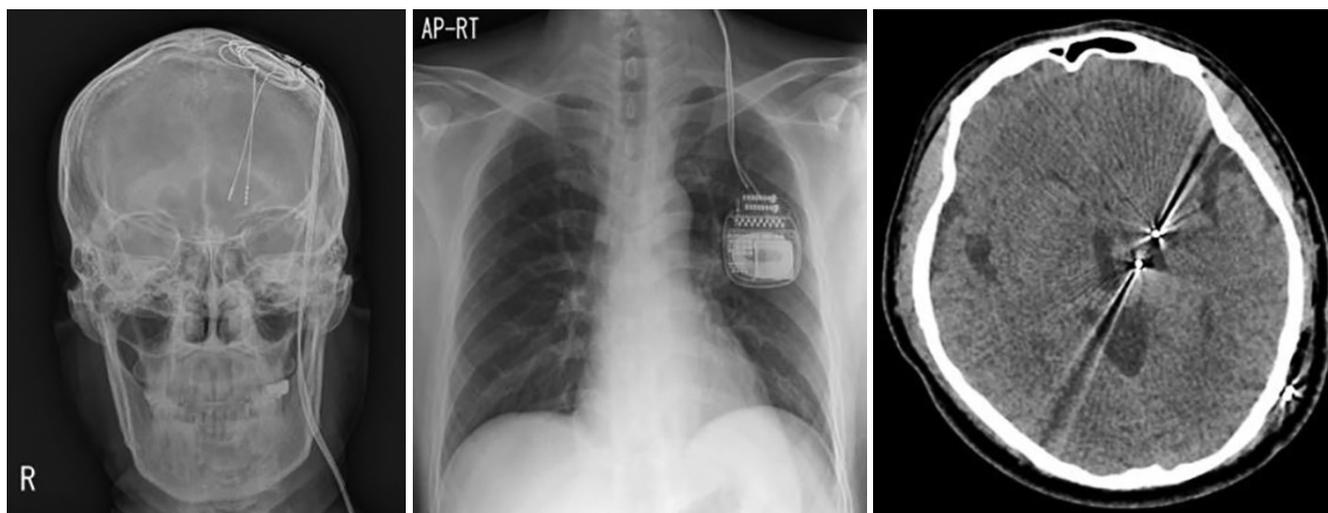


Fig. 3. Post-operative X-ray and CT images.

Table 1. Patient Demographic Data

Case no.	Symptom	Onset age (years)	Operation age (years)	Symptom duration (years)	Pre-operative BFMDRS	Post-operative 1-yr BFMDRS	Disability Scale	Post-operative 1-yr disability scale	f/u duration after operation (months)
1	Rt. upper extremity (shoulder contraction, distal arm rotation)	9	32	23	14	2	10	2	81
2	Lt. upper extremity (hand myoclonic jerk, distal arm tremor)	4	45	41	16	4	5	4	49
3	Rt. upper extremity (task-specific distal arm dystonia)	18	40	22	12	2	9	2	50
4	Lt. upper extremity (shoulder, arm)	5	53	48	33	24	6	4	28
5	Rt. upper extremity (finger)	41	49	8	12	0	2	0	12

BFMDRS, Burke-Fahn-Marsden Dystonia Rating Scale.

Table 2. Stimulation Contact and Parameters for Dual Pallidal and Thalamic Electrodes

Case no.	Post-operative 1-month stimulation parameters								Latest stimulation parameters							
	Gpi contact	V	uS	Hz	Vo contact	V	uS	Hz	Gpi contact	V	uS	Hz	Vo contact	V	uS	Hz
1	0, 1	2.6	60	70	0	2	60	130	0, 1	2.6	60	70	0	2	60	130
2	1, 2	1.8	150	160	1, 2	0.5	60	160	1, 2	1.6	120	170	1, 2	0.4	70	170
3	1, 2	2	80	160	1	3.2	80	160	1, 2	2	80	160	1	3	90	160
4	1, 2	1.8	90	160	2, 3	1.5	90	160	1, 2, 3	2	180	90	1, 2, 3	1.2	60	90
5	0, 1	1	90	60	1	2.2	60	160	Preserved	-	-	-	1	2.5	60	130

Gpi, globus pallidus pars interna; V, voltage; uS, pulse width; Hz, frequency; Vo, ventralis oralis.

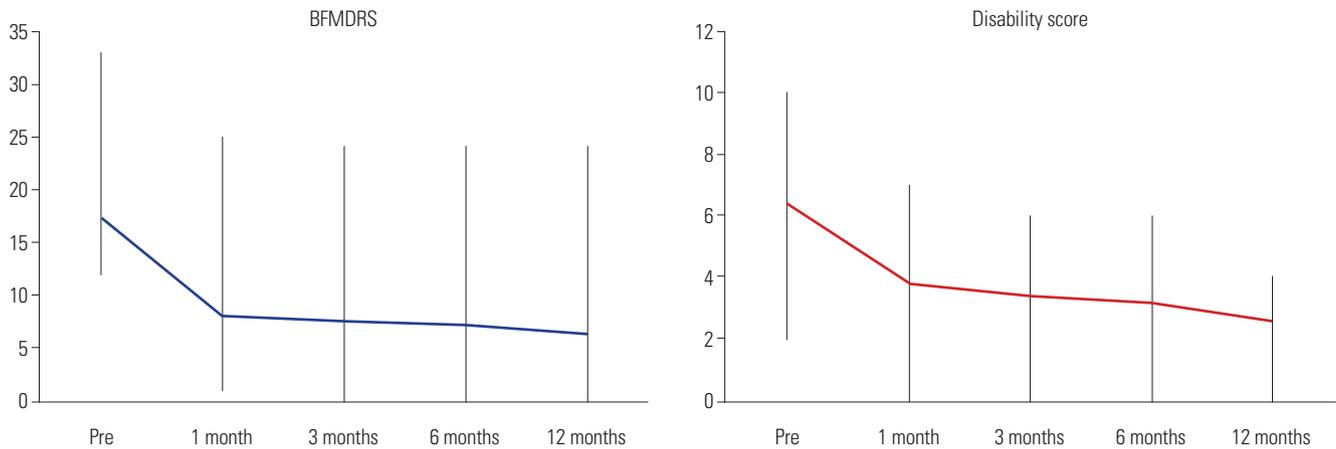


Fig. 4. Clinical outcome scores of dual pallidal and thalamic electrodes. BFMDRS, Burke-Fahn-Marsden Dystonia Rating Scale.

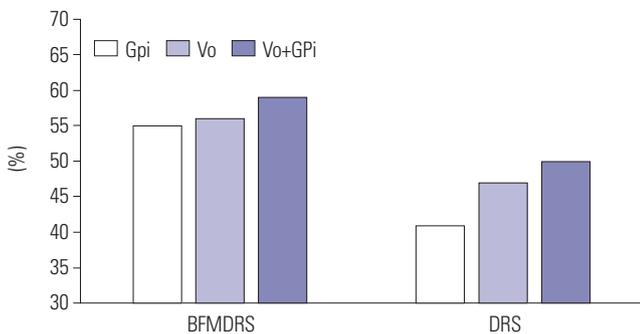


Fig. 5. Efficiency of dual stimulation. BFMDRS, Burke-Fahn-Marsden Dystonia Rating Scale; DRS, Disability Rating Scale; GPI, globus pallidus pars interna; Vo, ventralis oralis.

Scale scores were both 0 with solitary Vo stimulation. GPI contact stimulation was preserved for later use in case of symptom aggravation.

Compared to pre-operative scores, BFMDRS decreased by 55% at 1-month, 56% at 3-month, 59% at 6-month, and 64% at 12-month follow up. The difference in initial and final scores showed statistical significance ($p < 0.01$). Disability Rating Scale scores decreased 41% at 1-month, 47% at 3-month, 50% at 6-month, and 60% at 12-month follow up (Fig. 4), and the difference in initial and final scores showed statistical significance ($p < 0.05$). Comparing the benefit of a single target versus both targets at 1-month follow up (Fig. 5), we discovered that stimulating both targets (BFMDRS, 59% decrease; Disability Rating Scale, 50% decrease) was more beneficial than targeting the GPI (BFMDRS, 55% decrease; Disability Rating Scale, 41% decrease) or Vo (BFMDRS, 56% decrease; Disability Rating Scale, 47% decrease) alone ($p < 0.01$).

DISCUSSION

Several randomized sham-controlled trials have now proven the efficacy of pallidal DBS for dystonia,⁵⁻⁸ and DBS now taken

as a major place in the treatment of dystonia.⁸ The mechanisms of how DBS achieves a clinical effect in dystonia are complex. Stimulations might inhibit the pathological activity of the basal ganglia-cerebello-thalamo-cortical circuit. However, patients often show delayed and progressive improvement over weeks to months to achieve an optimal benefit. Some suggest that this might stem from progressive motor learning and modification of maladaptive plasticity.²⁴ However, after this slow improvement, it seems that long-term stimulation produces long lasting changes, supporting DBS as a disease modifying treatment in dystonia.^{8,12,24}

Till now, the GPI has been the most established target for DBS in dystonia.⁵ Stimulation of the GPI elicits significant improvement in many symptoms of dystonia with less adverse effects.¹² However, in some patients, bradykinesia and gait problems have been found in those who have achieved a good response to DBS, although this is not fully understood.^{5,8,9} These adverse effects usually can be modulated by reducing the stimulation and making a compromise between side effect and benefit.¹² Therefore, additional targets for DBS are under research for dystonia, such as the subthalamic nucleus and the thalamus.^{13-16,20,22,25} The sensorimotor thalamus is a new interesting target area for DBS, which was once regarded as the standard target for radiofrequency lesioning in dystonia.²⁶ There are studies seeking to identify which region in the ventrolateral thalamus (ventral-oralis anterior, ventral-oralis posterior, or Vim) would be an ideal target for DBS.^{13,20-23} The Vo complex nucleus plays a key role in the motor function related with the basal ganglia-cerebello-thalamo-cortical circuit.^{1,4,18,27} The pallidothalamic pathway involves both the GPI and Vo, and therefore, targeting both might provide more benefits.²⁸ Indeed, targeting the Vo complex has been found to elicit benefits in dystonic tremor or focal dystonia in previous studies and to sometimes show superiority over targeting only the GPI.^{22,28-30}

In this study, we performed unilateral DBS targeting the GPI and Vo in patients with dystonia. After the DBS patients were stimulated at either the GPI or Vo alone, we compared clinical

scores for each target. With GPi stimulation alone, dystonic posture improved, although dystonic tremors were still observed. With Vo stimulation alone, benefits were less than optimal. However, stimulating both targets elicited maximal improvement in BFMDRS and disability scores. For example, in Case 2, although Vo stimulation was turned on at a minimal level during the dual stimulation, the patient presented better improvement in tremor symptoms than GPi stimulation alone. Notwithstanding, we only compared single and dual stimulation at 1-month post-operation in the patient group, which is somewhat insufficient to derive a definite advantage. As such, we also reviewed previous clinical results from our institute and compared the long-term efficiency of DBS in focal dystonia patients between GPi-Vo dual stimulation and GPi single stimulation. In the single target stimulation, the average BFMDRS score decreased 54%, and disability score decreased 16%, whereas dual stimulation decreased scores 59% and 50%, respectively. This suggests that dual electrode stimulation at both GPi and Vo targets in the unilateral brain for patients with unilateral focal or segmental dystonic symptoms might be beneficial.

In conclusion, unilateral thalamic and pallidal dual electrode DBS may be effective or even superior to single target for dystonia. Although the number of patients in this study was small, the clinical outcomes were favorable.

AUTHOR CONTRIBUTIONS

Conceptualization: Jin Woo Chang. **Data curation:** Kyung Won Chang. **Formal analysis:** Kyung won Chang. **Funding acquisition:** So Hee Park. **Investigation:** Myung Ji Kim. **Methodology:** Jin Woo Chang. **Project administration:** Jin Woo Chang. **Resources:** Jin Woo Chang. **Software:** Kyung Won Chang. **Supervision:** Won Seok Chang, Hyun Ho Jung, and Jin Woo Chang. **Validation:** Jin Woo Chang. **Visualization:** Kyung Won Chang. **Writing—original draft:** Kyung Won Chang. **Writing—review & editing:** Kyung Won Chang and Jin Woo Chang. **Approval of final manuscript:** all authors.

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