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Preliminary results from this work have been presented at the following: Honey CR et al. "The Neurosurgical Treatment of Spasmodic Dysphonia: Preliminary results of a Prospective, Randomized, Sham-Controlled (DEBUSSY) Trial" at the XXIII Congress of the European Society for Stereotactic and Functional Neurosurgery, as a podium presentation, on September 27, 2018, Edinburgh, United Kingdom; and Honey CR. "Challenging Neurosurgical Dogma," The Sir Victor Horsley Lecture (2019) at the National Hospital for Neurology and Neurosurgery, Queen Square, London, December 5, 2019.

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Thalamic Deep Brain Stimulation for Spasmodic Dysphonia: A Phase I Prospective Randomized Double-Blind Crossover Trial

BACKGROUND: Adductor spasmodic dysphonia (SD) is a dystonia of the vocal folds causing difficulty with speech. The current standard of care is repeated botulinum toxin injections to weaken the adductor muscles. We sought to ameliorate the underlying neurological cause of SD with a novel therapy—deep brain stimulation (DBS).

OBJECTIVE: To assess the safety of DBS in SD through phase I trial, and to quantify the magnitude of any benefit.

METHODS: Six patients had left ventral intermediate nucleus (Vim) thalamic DBS and were randomized to 3 mo blinded-DBS "on" or "off" followed by a crossover. Primary outcomes were quality of life and quality of voice during the blinded phase. Patients continued with open-DBS "on." Secondary outcomes were comparisons of pre- and 1-yr cognitive, mood, and quality of life. This trial was registered with ClinicalTrials.gov (NCT02558634).

RESULTS: There were no complications. Every patient reported an improvement in quality of life ($P = .07$) and had an improvement in quality of their voice ($P = .06$) when their blinded DBS was "on" versus "off." The trend did not reach statistical significance with the small sample size. Secondary outcomes showed no difference in cognition, an improvement in mood, and quality of life at 1 yr.

CONCLUSION: This phase I randomized controlled trial confirmed that DBS can be performed safely in patients with SD. Blinded DBS produced a strong trend toward improved quality of life and objective quality of voice despite the small sample size. The cerebellar circuit, not the pallidal circuit, appears to be crucial for motor control of the vocal folds.

KEY WORDS: Deep brain stimulation, Randomized control trial, Spasmodic dysphonia, Quality of life

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Adductor spasmodic dysphonia (SD) is a neurological disorder of the voice compromising a patient's ability to speak due to involuntary contractions of the laryngeal muscles.[1] It is a task-specific, focal dystonia affecting approximately 1 to 4/100 000/yr.[2] Since the 1980s, the standard of care has been repeated botulinum toxin A injections in the affected muscles.[3] Botulinum toxin injections have limitations, including its expected temporary benefit, delayed onset and fading effect, neutralizing antibodies, and it is a repeatedly painful procedure.[4-6] Surgery to deliberately damage laryngeal function has poor results.[7-10] These approaches, mimicking the early treatments for cervical dystonia, ignore the underlying neurological dysfunction underpinning SD. Several lines of evidence suggested to us that SD might be effectively treated with a novel therapy for this condition—deep brain stimulation (DBS).

ABBREVIATIONS: BDI-II, Beck Depression Inventory version II; **CONSORT,** Consolidated Standards of Reporting Trials; **LCN,** local circuit neuron; **LMC,** laryngeal motor cortex; **MoCA,** Montreal Cognitive Assessment; **SD,** spasmodic dysphonia; **SMA,** supplementary motor area; **Vim,** ventral intermediate nucleus; **USDRS,** Unified Spasmodic Dysphonia Rating Scale; **VHI,** Voice Handicap Index; **VOA,** Ventral oralis anterior; **V-RQOL,** Voice-Related Quality of Life measure

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First, many other forms of dystonia have been successfully treated with DBS.[11,12] Second, a retrospective review of our data base revealed 2 patients with concomitant essential tremor and SD. Both reported unexpected benefits in their voice following the surgery for their tremor (unreported). Third, one of our patients with concurrent essential tremor and SD was assessed in a prospective, randomized, double-blinded trial of one and was found to have obvious improvement in their voice with DBS "on" compared to DBS "off."[13] These results led us to design and undertake this phase I trial to assess the safety and degree of efficacy of DBS for SD. We chose unilateral left ventral intermediate nucleus (Vim) thalamic DBS because blinded assessment of 3 previous patients with thalamic DBS for essential tremor and concomitant SD showed that left unilateral or bilateral stimulation produced equal benefits for voice and unilateral surgery was felt to be safer.

METHODS

Trial Design and Setting

The protocol for this prospective, randomized, double-blinded, crossover trial was published on the clinicaltrials.gov website (NCT02558634) before the recruitment of any patients. Ethical permission for this study was obtained from our university's Clinical Research Ethics Board (H15-02535) and informed patient consent was obtained. We have followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines for reporting randomized crossover trials.[14,15] The trial was conducted in an academic university setting.

Patients

A subset of patients with severe symptoms attending our SD clinic were contacted by letter and asked if they wanted to participate in this research trial. All had adductor SD previously diagnosed by consensus among 2 laryngologists and a speech-language pathologist (see **Text**, **Supplemental Digital Content 1**, for diagnosis).

Surgery and DBS Optimization

All patients had a single lead model 3389-40 (Medtronic), inserted into their left thalamic Vim.[13] Target coordinates were anterior: 25% of the anterior commissure-posterior commissure (AC-PC) distance anterior to PC; lateral: 10 mm from the edge of the ventricle; and vertical = 0 mm. The anterior coordinate was adjusted intraoperatively so macrostimulation with TC-16-2-250-D (Cosman Medical), 50 Hz, 1 ms caused paresthesia at 0.8 to 1.5 V. An implantable neural stimulator, Activa SC (Medtronic), was placed under general anesthetic during the same operation in the chest or abdomen depending on patient preference. Postoperative computed tomography (CT) was performed the following day, and all patients were discharged home on the first or second postoperative day. DBS parameter adjustments began 4 wk after surgery and were optimized during multiple sessions over the following month. We began with a "monopolar review" testing each contact (185 Hz, 60 μs) to determine the voltage threshold for clinical benefit and side effect. Benefit was determined both subjectively by the patients reporting ease of speech and objectively by the nurses assessing clarity of speech. Once the optimum contacts were determined, additional comparative tests were made with longer pulse widths and in bipolar settings. Stimulation parameters with side effects (eg, paresthesia or dysarthria) were not allowed to avoid unblinding the patients. Once optimized, patients were then randomized.

Randomization and Masking

A computer-generated random number was used to place each patient into 1 of 2 groups. Group ON-OFF received 3 mo of DBS stimulation followed by 3 mo without stimulation; group OFF-ON received the opposite combination. Patients and assessors were blinded to the DBS setting. After 6 mo, all patients continued with unblinded DBS "on" for an additional 6 mo. Patients could ask at any time to be unblinded or exit the trial.

Primary Outcomes

Two primary endpoints were selected and published (clinicaltrials.gov) before the trial began. At the end of each 3-mo blinded period, the patients subjectively rated their quality of life with the Voice-Related Quality of Life measure (V-RQOL),[16] and the quality of their voice was objectively rated by 2 experienced speech-language pathologists using the overall component of the Unified Spasmodic Dysphonia Rating Scale (USDRS)[17] (see **Text**, **Supplemental Digital Content 2**, for details of tests).

Secondary Outcomes

Additional secondary outcome measures were taken to generate hypotheses for future studies. These included comparisons during the unblinded portion of the study comparing preoperative and 1-yr assessments of V-RQOL and an additional self-report tool, the Voice Handicap Index (VHI).[18] Finally, patients were also asked at the conclusion of the study, "Knowing what you now know, would you have the surgery or recommend it to a family member?"

Safety Assessment

All patients were clinically assessed immediately postoperatively, on postoperative day 1 (and day 2 if still in hospital), weekly during stimulation adjustment, and then at 3, 6, and 12 mo. Examinations were tailored to find new neurological deficits, wound infections, and technical malfunctions. Additional tests were conducted to assess cognition (Montreal Cognitive Assessment [MoCA]) and mood (Beck Depression Inventory version II [BDI-II]) before and at the conclusion of the trial. All patients had CT head imaging on postoperative day 1.

Statistical Analysis

The randomized comparison between DBS ON-OFF and OFF-ON for the 2 primary outcomes were compared with the Wilcoxon rank sum test for nonparametric repeated measures. The median effect size, with associated exact 95% CI, was computed using the Hodges-Lehmann method. The level of significance was set at $P = .025$ to allow a Bonferroni correction for these 2 tests. Multiple secondary nonrandomized comparisons were performed as a hypothesis generating exercise

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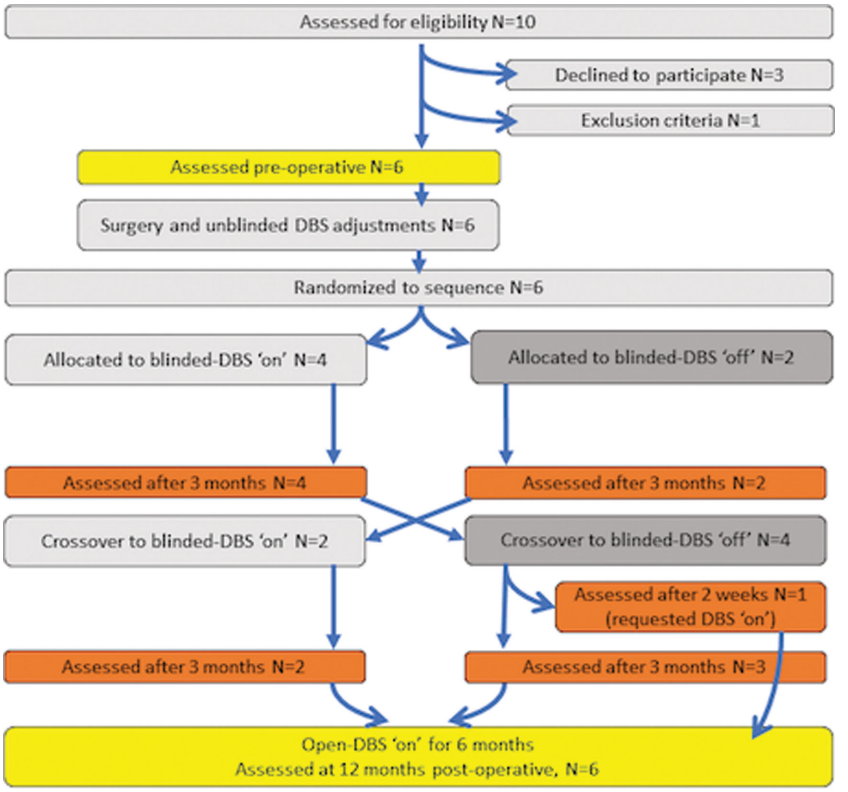

FIGURE 1. *Trial profile. Flow diagram for the randomized clinical crossover trial. Primary analyses were during the blinded phase (orange) and secondary analyses during the open phase (yellow).*

using the Wilcoxon signed-rank test to assess for differences in V-RQOL, VHI, MoCA, and BDI-II between paired preoperative and 1-yr postoperative unblinded assessments for each participant. Statistics were calculated using SPSS v.25 software (IBM).

Data Availability

The data for this study will be made available with publication at Mendeley Data (Elsevier). Available data will include deidentified participant data and a data dictionary defining each field in the set.

RESULTS

The trial profile is presented in Figure 1. Ten patients were contacted and 6 (5 women) were enrolled in the study between January 1, 2017, and May 30, 2018, and followed postoperatively for 1 yr. The demographic data for the cohort are presented in Table 1. The lead tip location and final stimulation parameters are presented in Table 2. The benefit of DBS stimulation was immediately obvious to the patients and the DBS nurses. In retrospect, all 6 patients correctly guessed which blinded group they were in. One patient asked to be unblinded following a perceived worsening of their voice with their crossover to the blinded-DBS "off" setting and their scores were analyzed following an intention to treat. It was possible to detect a clinical benefit within seconds of stimulation activation or almost immediately after adjusting to a better setting. Some settings were reported as obviously better by the patient but could not be distinguished by the nurse (this was an unexpected but important point, see Discussion section).

Primary Outcomes

Subjective quality of life (V-RQOL) was compared after 3 mo of blinded stimulation. Each patient improved with DBS "on" compared to "off." The median effect size was 55.7 (95% CI 33.5, 63.5, $P = .07$) and was enough to improve the cohort's median score by 2 categories from "poor" to "good." Figure 2 shows the results for the V-RQOL scores before surgery, with blinded-DBS "on," blinded-DBS "off," and at 1-yr open-DBS "on." Figure 3 shows the individual scores for each patient with blinded-DBS "off" and "on."

Objective measure of quality of voice (overall severity component of the USDRS) was compared after 3 mo of blinded stimulation. Each patient improved with DBS "on" compared to "off." The median effect size was −1.25 (95% CI −0.75, −1.75, $P = .06$), with lower scores better. Figure 4 shows the results for USDRS scores before surgery, with blinded-DBS "on,"

TABLE 1. Demographics of the Cohort

				Preoperative evaluation						
						USDRS				
Patient	Age/gender	Years with SD	Randomization	V-RQOL	VHI	Over-all	VT	MoCA	BDI-II	Employed
1	59/F	23	ON-OFF	15	97	2.5	2	25	20	Yes
2	76/F	22	ON-OFF	25	106	6	3	23	10	Retired
3	54/F	10	OFF-ON	25	95	3	2.5	27	21	Dis.
4	69/F	30	OFF-ON	30	65	4.5	1	18	5	Retired
5	59/F	2[a]	ON-OFF	8	79	4	3.5	27	18	Yes
6	74/M	30	ON-OFF	39	67	3	1	25	6	Retired

DBI-II = Beck Depression Index version II (0-63, below 13 is "minimal"); Dis. = disabled from working due to voice; F = female; M = male; MoCA = Montreal Cognitive Assessment (0-30, ≥26 is normal); USDRS = Unified Spasmodic Dysphonia Rating Scale (results averaged from 2 assessors) with overall component (0-7, higher worse); VHI = Voice Handicap Index (0-120, above 60 is "severe"); V-RQOL = Voice-Related Quality of Life measure (0-100, below 50 is "poor"); VT = vocal tremor component (0-7, higher worse).
[a]Voice disorder for 9 yr with a diagnosis of SD for 2 yr.

TABLE 2. Electrode Tip Location and Stimulation Parameters

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Left lead tip	X = −11.7 Y = −4.1 Z = −1.0	X = −11.4 Y = −6.6 Z = −0.5	X = −11.6 Y = −6.5 Z = 0.1	X = −10.7 Y = −5.3 Z = 0.1	X = −11.1 Y = −3.8 Z = 0.0	X = −12.0 Y = −6.4 Z = −1.0
Coronal	17°	20°	16°	23°	14°	22°
Sagittal	56°	58°	60°	64°	64°	58°
Contacts	0−, 1+	C+, 0−	C+, 1−	C+, 1−	0+, 1−	C+, 1−
Frequency	185 Hz	185 Hz	185 Hz	185 Hz	185 Hz	185 Hz
Pulse width	90 μs	90 μs	90 μs	60 μs	60 μs	60 μs
Voltage	1.5 V	2.1 V	3.5 V	2.0 V	1.3 V	2.6 V

Coordinates of the electrode tip are provided relative to the mid-commissural point with x = lateral, y = anterior, and z = vertical distances in millimeters. Electrode trajectory angles are presented in the coronal plane (vertical approach = 0°) and sagittal plane (vertical = 90°). Stimulation parameters are provided with the deepest contact labeled "0" and c = case (for monopolar stimulation).

blinded-DBS "off," and at 1-yr open-DBS "on." Figure 5 shows the individual scores for each patient with blinded-DBS "off" and "on."

Secondary Outcomes

Individual paired comparisons were made with Wilcoxon signed-rank test. These comparisons were not subjected to a Bonferroni correction because they were designed to generate hypotheses not to answer our primary objectives. The patient-perceived voice handicap (VHI) was better ($P = .028$) during blinded-DBS "on" compared to blinded-DBS "off." The 1-yr open-DBS "on" was also better ($P = .027$) than the preoperative time point. Figure 6 shows the VHI scores before surgery, with blinded-DBS "on," blinded-DBS "off," and at 1-yr open-DBS "on." The patients' quality of life (V-RQOL) was better ($P = .028$) with the open-DBS "on" than preoperatively. At the conclusion of the trial, all the patients reported that they would have the surgery again or recommend it to a family member.

Safety

None of the patients had any adverse or unexpected clinical events during the trial and no asymptomatic hemorrhages were detected. The cognitive ability of the patients was evaluated preoperatively and at the end of the 1-yr study with the MoCA and compared with the Wilcoxon signed-rank test. The median and interquartile range for the cohort preoperatively (25, 21.8-27) and at the 1-yr follow-up (27.5, 25.3-29) were not significantly different. The mood of the patients was evaluated preoperatively and at the end of the 1-yr study with the BDI-II and compared with the Wilcoxon signed-rank test. The median and interquartile range for the cohort at the 1-yr follow-up (4.5, 0.8-14.2) were better ($P = .027$) than at the preoperative evaluation (14, 5.8-20.2).

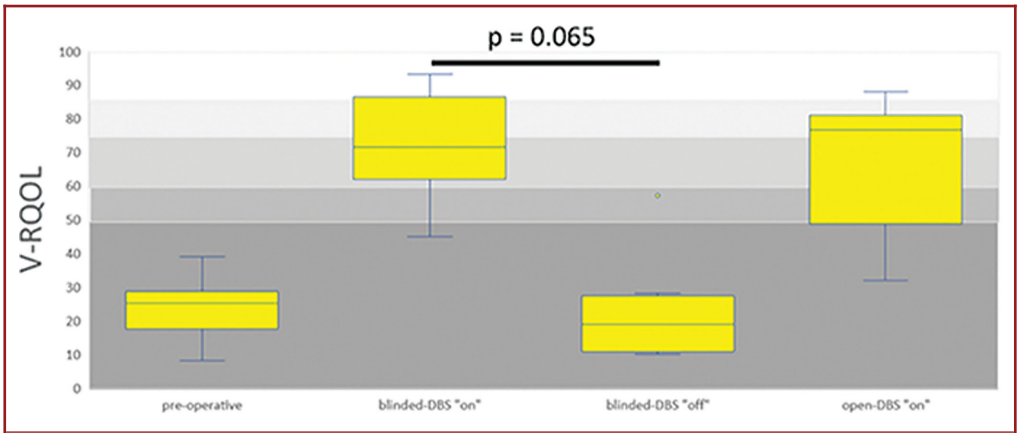

FIGURE 2. *Quality of life. Box plot of the median and interquartile range of the V-RQOL for the cohort during each of the 4 experimental settings. Higher scores are better with scores below 50 considered "poor," 51 to 60 "fair," 61 to 75 "good," 76 to 85 "very good," above 85 "excellent." In the blinded phase of the study, the median effect size was 55.7 with the 95% CI 33.5 to 63.5. This effect size was enough to improve the cohort's median score of 2 categories from "poor" to "good." The randomized comparison of DBS ON-OFF and OFF-ON was not significant.*

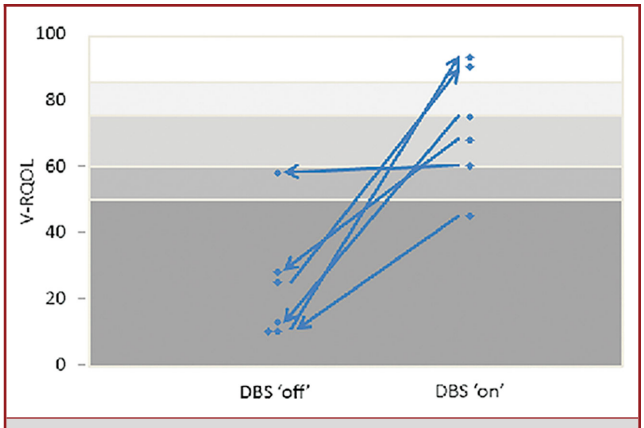

FIGURE 3. *Changes in individual quality of life scores during blinded-DBS "off" and "on." The V-RQOL for each subject following 3 mo of blinded-DBS "off" and "on." Higher scores are better with score below 50 considered "poor," 51 to 60 "fair," 61 to 74 "good," 75 to 85 "very good," and above 85 "excellent." Arrows show the sequence of randomization.*

DISCUSSION

This phase I randomized controlled trial demonstrated that unilateral thalamic DBS could be safely performed in patients with adductor SD. Although there were no complications in this cohort, the risk of this surgery likely parallels that of thalamic DBS for essential tremor.[19]

During the blinded phase of this trial, each patient reported an improvement in their quality of life (V-RQOL) when the thalamic DBS was turned "on" compared to when it was "off." The median effect size was sufficient to improve the cohort's V-RQOL by 2 categories from "poor" to "good." This trend in improvement did not reach statistical significance ($P = .065$) in our small cohort. A power calculation revealed that 10 patients would be needed in a phase II trial to have a 90% chance of detecting a difference between the means of the treatment and control groups. Each patient also had an objective improvement in the quality of their voice (overall component of the USDRS) when the blinded DBS was "on" compared to "off." This trend did not reach statistical significance ($P = .057$).

There was a reduction in depression, which may reflect satisfaction with the treatment protocol but would require a future study to confirm. All 6 patients reported at the conclusion of the trial that, "Knowing what they now know, they would have the surgery again or refer a family member."

The surgery was performed unilaterally because our previous work had demonstrated a marked lateralized effect on voice with thalamic DBS and we wanted to reduce the risks of surgery for this phase I trial.[13,20] Recent work has shown that bilateral surgery may add a small but additional benefit to the voice.[21]

There were several weaknesses in the study. First, the blinding was unsuccessful because all the patients correctly guessed into which group they had been randomized. This reflected the magnitude of the clinical benefit—the voice change was obvious when the DBS was turned "on"—rather than a failure of randomization. Second, the metric used to quantify the quality of voice (overall component of the USDRS) may not have been ideal because, in order to blind the assessors from whether the patients had had surgery or not, recorded voice samples were used instead of interviews. This precluded any visual assessment of patients (eg, associated movements or effort). Patients also reported certain stimulation settings were subjectively better for their voice without the observers noticing any objective changes. This may reflect an easing of the patient's internal effort required to speak rather than the quality of sounds being produced. This

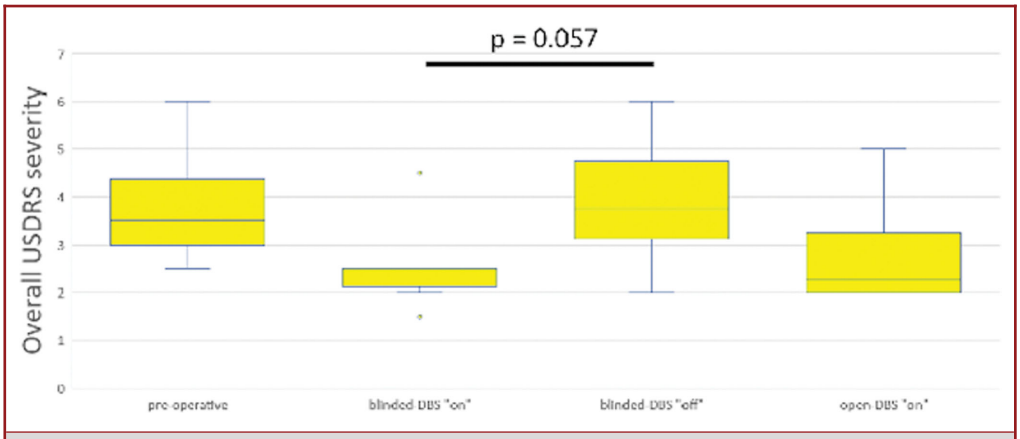

FIGURE 4. *Quality of voice. Box plot of the median and interquartile range of the overall severity component of the USDRS for the cohort during each of the 4 experimental settings. Lower scores are better. In the blinded phase of the study, the median effect size was 1.25. The randomized comparison of DBS ON-OFF and OFF-ON was not significant.*

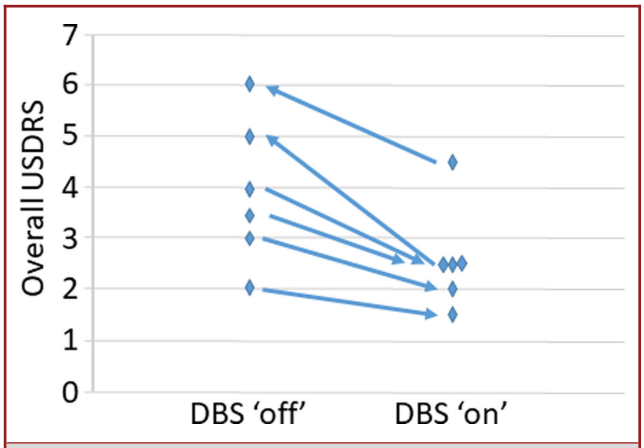

FIGURE 5. *Changes in individual quality of voice scores during blinded-DBS "off" and "on." The overall USDRS for each subject following 3 mo of blinded-DBS "off" and "on." Lower scores are better. Arrows show the sequence of randomization.*

is an important aspect for patients subjectively but apparently difficult to quantify objectively. Third, there was no wash-out phase in this crossover trial. We knew from our previous patients that the acute effects of DBS on SD had a rapid onset (seconds) and short carryover (minutes).

This study sheds light on the neural circuits underpinning speech and SD.[22]

The human laryngeal motor cortex (LMC), located in the most inferior portion of the precentral gyrus, controls the muscles required for speech. There are direct bilateral connections to the laryngeal motor neurons in the nucleus ambiguous from each LMC.[23] The sensory feedback required for speech is less well understood but may be critical in SD. Functional brain imaging studies and transcranial magnetic stimulation have demonstrated increased activity and cortical excitability in the LMC of patients with SD compared to normal controls.[24,25]

We now propose a model of the pathophysiology underpinning SD based on our clinical trial. The motor portion of the thalamus can be subdivided into regions which receive input from the cerebellum (Vim), pallidum (Ventral oralis anterior (Voa)), and nigra (Lateropolaris).[26] This study demonstrated the clinical benefit of Vim DBS in SD. The lack of benefit from either pallidal[12] or Voa[13] DBS suggests that the cerebellar circuit not the pallidal circuit is involved in SD. The primary locus of pathophysiology in SD should therefore lie within this circuit—in the cerebellum, thalamic Vim, or LMC.

The thalamic Vim receives excitatory input from the deep cerebellar nuclei (primarily the dentate nucleus) as well as the motor and premotor cortices. It receives inhibitory GABAergic input from thalamic local circuit neurons (LCN) and the thalamic reticular nucleus.[27] It has excitatory thalamocortical projections to the motor cortex (containing the LMC) as well as the premotor cortex, supplementary motor area (SMA), and pre-SMA.

We speculate that overactivity of the Vim thalamocortical excitatory projection neurons could pathologically excite the LMC resulting in diffuse activation of the laryngeal musculature. Thalamic Vim DBS may downregulate this by activating the GABAergic LCN neurons (and/or the reticular nucleus axons).

If this model is correct, SD should be improved by increased cerebellar cortical activity (eg, transcranial magnetic stimulation of the right cerebellum which would reduce deep cerebellar nuclear output to Vim), reduced thalamic activity (eg, left Vim DBS or thalamotomy), or any medication that inhibits excitatory neurons. Neuromodulation of the cerebellum has shown benefit in focal dystonia but has not yet been tried in SD.[28] A small open-label study has demonstrated temporary benefits for SD following oral sodium oxybate, a GABA precursor.[29]

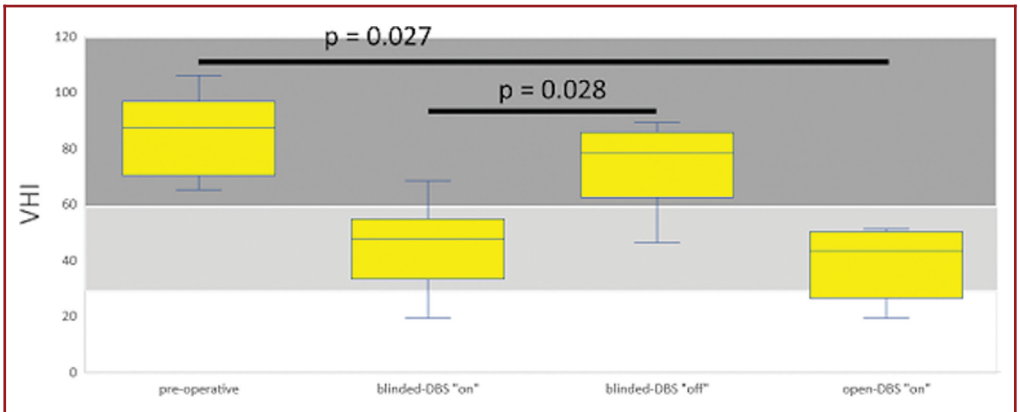

FIGURE 6. *Patient perceived voice handicap measured by the VHI. Box plot of the median and interquartile range of the VHI for the cohort during each of the 4 experimental settings. Lower scores are better with below 30 considered "minimal," 31 to 60 "moderate," and above 60 "severe." Patients had better scores (P = .028) during the blinded-DBS "on" than the blinded-DBS "off." Patients also had better scores (P = .027) at the 1-yr open-DBS "on" timepoint compared to their preoperative evaluation.*

CONCLUSION

This phase I, prospective, randomized, crossover trial demonstrated that unilateral thalamic DBS can be performed safely in a cohort of patients with SD. During the blinded phase of this trial, each patient reported a subjective improvement in their quality of life and their voice was objectively assessed as improved when their thalamic DBS was "on" compared to "off." This trend did not reach statistical significance but the data allow a power calculation for a phase II trial. The results provide insights into the pathophysiology underpinning SD and the neurophysiology of speech.

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Disclosures

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Supplemental Digital Content 1. Text. Diagnosis of adductor spasmodic dysphonia. The details of how the diagnosis of spasmodic dysphonia was made are presented.

Supplemental Digital Content 2. Text. Primary outcome measures. The 2 primary outcome measures, Voice-Related Quality Of Life and Unified Spasmodic Dysphonia Rating Scale, are described in detail.

COMMENT

The authors report on a small but rigorous clinical trial of thalamic deep brain stimulation for the management of spasmodic dysphonia. The study included 6 patients who were treated with left thalamic deep brain stimulation and then underwent a prospective, randomized, double blinded, crossover study. The DBS programming was conducted over several sessions starting at least 4 weeks after implantation surgery. The primary outcome measures were the voice-related quality of life tool (subjective) as well as objective assessment by 2 experienced speech pathologists rating on the unified spasmodic dysphonia rating scale.

The surgery as well as the stimulation were well tolerated. All patients reported improvements during active DBS compared to the OFF-DBS phase. Objective measurements by the speech pathologists also indicate improvements associated with active DBS.

This is an interesting study that addresses a rare neurological condition that does not have a good long-term solution. The results indicate that deep brain stimulation is safe in this patient population and suggest effectiveness. The lack of statistically significant differences should be interpreted in the context that this is a rare disease. It is difficult – if not impossible – to conduct larger randomized controlled trials in orphan diseases. The magnitude of the effect is encouraging and suggests that the authors have identified a viable treatment for this patient population.

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