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PAllidal versus SubThalamic deep brain Stimulation for Cervical Dystonia (PASTS-CD): study protocol for a multicenter randomized controlled trial

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Title: PAllidal versus SubThalamic deep brain Stimulation for Cervical Dystonia (PASTS-CD): study protocol for a multicenter randomized controlled trial

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ABSTRACT

Introduction Deep brain stimulation (DBS) has been validated as a safe and effective treatment for refractory cervical dystonia (CD). Globus pallidus internus (GPi) and subthalamic nucleus (STN) are two main stimulating targets. However, there has been no prospective study to clarify which target is the better DBS candidate for CD. The objective of this trial is to compare directly the efficacy and safety of GPi-DBS and STN-DBS, thereby instructing the selection of DBS target in clinical practice.

Methods and analysis This multicenter, prospective, randomized, controlled study plans to enroll 98 refractory CD patients. Eligible CD patients will be randomly allocated to GPi-DBS group or STN-DBS group, with the DBS electrodes implanted into the posteroventral portion of GPi or the dorsolateral portion of STN, respectively. The primary outcome will be the improvement of symptomatic severity, measured by the changes of Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) severity subscale and Tsui scale at 1 month, 3 months, 6 months, and 12 months after surgery. The secondary outcomes include the improvement of TWSTRS-disability subscale, TWSTRS-pain subscale, quality of life, mental and cognitive condition, as well as the differences of stimulation parameters and adverse effects. In addition, this study intends to identify certain predictors of DBS efficacy for CD.

Ethics and dissemination The trial has been approved by the Medical Ethics Committee of Chinese PLA General Hospital (S2022-613-01). The results of this study will be published in international peer-reviewed journals and shared in professional medical conferences.

Trial registration numbers NCT05715138

Key Words cervical dystonia, deep brain stimulation, globus pallidus internus, subthalamic nucleus.

ARTICLE SUMMARY

Strengths and limitations of this study

The PASTS-CD study is the first randomized controlled study comparing the efficacy and safety of GPi-DBS and STN-DBS for cervical dystonia.

The primary outcomes are evaluated blindly through randomly shuffled, de-identified, standardized videos to minimize potential biases.

This trial uses the technique of imaging fusion to control the confounder of electrodes position, which is deemed to be the major influence factor of DBS efficacy.

One possible limitation is that investigators are not blinded because of the nature of surgical intervention.

INTRODUCTION

Background and rationale

Cervical dystonia (CD), also known as spasmodic torticollis, is a type of focal dystonia, mainly manifesting as involuntary head turning or tilting, or holding a prolonged and twisted posture.[1, 2] CD limits the neck activity by involving one or a group of neck muscles and is often accompanied by pain and psychological disorders, seriously compromising patients' life quality.[2]

Medical treatment of CD is unsatisfactory. Oral medications are often ineffective or overshadowed by concomitant side effects.[2] Although most of CD patients can be alleviated by injection of botulinum toxin, the remission is temporary so that patients require multiple injections.[3] Moreover, 25% of patients do not respond to botulinum toxin and 20%-40% of patients discontinued botulinum toxin treatment due to lack of benefit.[4, 5] Denervation and myotomy of the involved muscles is an effective surgery for CD once, but it becomes powerless in face of complicated cases.[6]

Deep brain stimulation (DBS) has been substantiated to be a safe and effective therapy for primary CD, even for those medically refractory cases.[7] The globus pallidus internus (GPi) was considered as the preferred DBS target for various types of dystonia (including CD) with remarkable short-term and long-term efficacy.[7-16] In addition, stimulation of the subthalamic nucleus (STN) has drawn increasing attention in recent years with the superiorities of lower stimulation parameters requirement and shorter onset time. A series of studies have demonstrated that STN-DBS is a promising alternative to GPi-DBS, with a long-term symptomatic improvement rate ranging from 50% to 90%,[17-21] similar to and even higher than that of GPi-DBS. For studies focusing on CD only, both GPi-DBS[10, 22-27] and STN-DBS[17, 28, 29] show significant therapeutic effect. However, the question of which nucleus is the better DBS candidate for CD has not been clarified.

Previous comparisons of both targets were mainly about dystonia as a whole (including focal, segmental, and generalized dystonia). There was a prospective crossover study directly comparing the efficacy and safety of GPi-DBS and STN-DBS by implanting two sets of DBS electrodes for each dystonic patient and stimulating alternately one of them.[30, 31] The results seemed to favor STN-DBS at the 6-month follow-up,[30] but no significant between-group difference was found at the over ten-years follow-up.[31] Furthermore, another crossover study evaluated the effect of 24-hour stimulation of either STN or GPi for eight dystonic patients and also found no significant between-group difference.[32] Retrospectively, STN-DBS was proven to outperform GPi-DBS in terms of movement improvement at the 1-month follow-up, but this superiority disappeared later, and at the 12-month follow-up, GPi-DBS was more efficient than STN-DBS in treatment of axial symptoms.[33] Moreover, another meta-regression analysis indicated that STN-DBS, relative to GPi-DBS, is associated with a better outcome in the univariate regression model but not in the multivariate model.[34] However, these studies did not distinguish specific phenotypes (not focus on CD). Additionally, the prospective studies were degraged by their small sample size and the retrospective analyses yielded inconsistent results.

For CD specifically, there have been no prospective studies to compare GPi-DBS with STN-DBS. From a retrospective perspective, a meta-analysis comparatively analyzed the results of 13 relative studies, including 58 CD patients undergoing GPi-DBS and 28 CD patients undergoing STN-DBS.[35] They found that when the factor of follow-up time was not taken into account, the improvement rates of the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) subscores (severity, disability, and pain) were all significantly higher in the GPi-DBS group than that in the STN-DBS group, though the TWSTRS total score was not significantly different. Nevertheless, when the follow-up time was limited within three years, neither TWSTRS total score nor subscores showed a significantly between-group difference.[35] Similarly, another meta-analysis also failed to detect any significant difference —— the improvement rates of the TWSTRS total score were 60.4% (GPi-DBS) and 56.6% (STN-DBS), respectively (p=0.936).[36] However, the two meta-analyses included low-quality studies and showed significant heterogeneity and publication bias. Surgeons still have confusions in face of target selection before surgery. As such, a well-designed randomized controlled trial (RCT) is entailed to ascertain which one (STN or GPi) is the optimal DBS target for CD.

Objective

The PASTS-CD study aims to compare GPi-DBS with STN-DBS for drug-refractory CD in the following aspects: (1) improvement of dystonic symptoms (severity, disability, and pain), (2) improvement of life quality, mental status, and cognitive status, (3) stimulation parameters, (4)

adverse effects. In the end, the study intends to identify the potential factors that are associated with DBS efficacy in both groups.

METHODS AND ANALYSIS

Study design and setting

The PASTS-CD study is an investigator-initiated, multicenter, prospective, randomized, parallel-controlled equivalence clinical trial, following the rules of Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.[37] This study is composed of two paralleling arms with an allocation ratio of 1:1, both of which undergo the same procedures except for the difference in DBS target (GPi or STN). The flow chart of the trial is presented in figure 1. This study will be implemented from March 2023 to November 2026 in four tertiary hospitals in China. This study only incorporates hospitals that have been qualified in DBS surgery for more than 5 years with more than 20 DBS operations per year, and where DBS surgery-related complication rate is less than 5%. In addition, all investigators will go through a standardized training prior to trial initiation.

Participants

Recruitment

The investigators will post the recruitment announcement on the official website and WeChat account of each center. CD Patients who are willing to participate in the trial will visit the dystonic outpatient of each center.

Inclusion criteria

(1) Diagnosed as idiopathic or hereditary isolated CD;
(2) Severe functional impairment despite optimal medical management;
(3) No secondary causes of CD;
(4) Age 18-80 years old;
(5) Normal neurological examination except for dystonia;
(6) Normal brain MRI;
(7) The subject or their family members can fully understand the trial and sign the informed consent;
(8) Good compliance and willingness to receive regular follow-ups.

Exclusion criteria

(1) Diagnosed as secondary CD;
(2) CD with obvious trunk/limb involvement, or Meige syndrome;
(3) History of severe mental disorders, dementia, or epilepsy;
(4) Previous dystonia surgery (pallidotomy, thalamotomy, DBS, etc);
(5) Accompanied by other neurological diseases (Parkinson's disease, essential tremor, multiple sclerosis, stroke, etc);
(6) The patient has or needs other implantable devices (cardiac pacemakers, defibrillators, cochlear implants, spinal cord stimulators, etc);
(7) Pregnant women or women who are waiting to become pregnant during the trial;
(8) Poor health condition.

Dropout or suspension of the trial

(1) Postoperative infection that requires removal of DBS electrodes;
(2) Severe displacement of DBS electrodes position from the predefined targets (>3mm);
(3) Occurrence of severe adverse events or other serious diseases that interfere the efficacy

assessment;

(4) Loss to follow up;

(5) Requests from patients to withdraw from the trial;

Interventions

Baseline evaluation

For each eligible patient, the basic information, medical history, disease characteristics and medications will be recorded in the electronic medical record system in detail. Besides, physical examination, routine blood tests and MRI scanning are assigned before surgery. Every patient will be videotaped as per a standardized scheme (see supplementary material) at least 12 hours after drug withdrawal. This video will be collected to complete the TWSTRS-severtiy subscale and Tsui scale by two neurological raters blindly at the end of the trial. Moreover, TWSTRS-disability subscale, TWSTRS-pain subscale, 36-item Short Form General Health Survey (SF-36), Hamilton Anxiey Scale (HAMA), Hamilton Depression Scale (HAMD), Mini-Mental State Examination (MMSE), and Montreal Cognitive Assessment (MoCA) will also be completed before surgery. The timeline of data collection is shown in table 1. After signature of informed consent form, candidate patients will be randomized into GPi-DBS group or STN-DBS group.

DBS surgery

Certain minor differences in surgical procedures are allowed among involved centers, but some critical steps must keep in line with each other. Specifically, elaborate target/trajectory planning and precise image fusion of MRI and stereotactic CT scanning are warranted before surgery. According to the preference of each center, DBS electrodes can be implanted with the assistance of Leksell stereotactic frame or neurosurgical robot under local or general anesthesia. But microelectrode recording (MER) must be performed intraoperatively, even under general anesthesia —— on recording, the dosage of propofol has to be reduce so as not to affect neuronal discharges.[38] According to the randomized allocation, the corresponding quadripolar electrodes will be implanted into posteroventral GPi (GPi-DBS group) or dorsolateral STN (STN-DBS group), bilaterally. The implanted electrodes can be selected from anyone of the following three manufacturers: Medtronic (Minneapolis, USA), PINS Medical (Beijing, China) and SceneRay (Suzhou, China). Of note, in light of the volume difference of the two nuclei, electrodes with contact intervals of 1.5mm are chosen for GPi-DBS, but 0.5mm for STN-DBS. Furthermore, given that patients' heads are immobilized by the frame, intraoperative macrostimulation is not recommended. Afterwards, inserted leads will be fixed at the burr hole site and a rechargeable or a non-rechargeable implantable pulse generator (IPG) will be connected and implanted at the right subclavicular area subcutaneously.

Electrode position confirmation

If possible, an intraoperative MRI scanning is strongly recommended to verify the implantation accuracy. Otherwise, a postoperative MRI or CT scanning is compulsory before discharge from hospital. Via the Lead-DBS software,[39] the investigators coregister and normalize the preoperative and postoperative images, and locate the four contacts in terms of the artifacts on the postoperative images. In order to exclude the effect of electrode position on the DBS efficacy, if the deviating distance between the sensorimotor subregion (according to DISTAL Minimal atlas)[40] and the nearest contact of the electrodes exceeds 3mm (STN-DBS group) or 5mm (GPi-DBS group), the subject will be dropped out.

Follow-up

One month later, the DSB will be activated by a specialized DBS programmer in the outpatient department. To evaluate stimulation effects and adverse effects of both electrodes, all contacts will be screened in a monopolar model with voltage increasing gradually from 1V to 4V and pulse width and frequency kept at 60us and 130Hz. The optimal parameters will be documented and used for chronic stimulation. After the DBS activation and at the 3-month follow-up, a standardized video will be recorded and TWSTRS-disability and pain subscales are completed by a centrally-trained rater. At the 6-month and 12-month follow-ups, besides the standardized video and TWSTRS subscales, all the other scales (i.e. SF-36, HAMA, HAMD, MMSE, and MoCA) will also be evaluated (table 1). Of note, botulinum toxin injection is forbidden during the follow-up period and the patient should stop taking oral medication for 12 hours before each evaluation. Furthermore, throughout the implementation of the trial, all adverse effects must be handled in safety and documented in detail, regardless of surgery-derived, device-related, or stimulation-induced events. The initial stimulating setting can be modulated at any time when the patients feel unsatisfactory about the symptom control or encounter a stimulation-induced adverse effect.

Outcome measurements

The primary outcomes are the changes (improvement rates) of TWSTRS-severity subscale and Tsui scale at 1 month, 3 months, 6 months, and 12 months after surgery. The reason why these two scales are chosen as the primary outcomes is that both of them are obtained from standardized videos, while the TWSTRS disability and pain subscales can be acquired via questionnaire (no need for a standardized video). The Tsui scale is a rational complement to the TWSTRS-severity subscale by adding the assessment of head tremor.

The secondary outcomes are the changes (improvement rates) of TWSTRS-disability subscale and TWSTRS-pain subscale, the difference of stimulation parameters and adverse effects at 1 month, 3 months, 6 months, and 12 months after surgery, as well as SF-36 questionnaire, HAMA scale, HAMD scale, MMSE scale, and MoCA scale at 6 months and 12 months after surgery. Stimulation parameters are mirrored by the total electrical energy delivered (TEED = voltage^2 * pulse width * frequency *1 second / impedance).[41] The higher the TEED, the shorter the battery life of stimulator. The improvement rate of each scale can be calculated by the following formula: (score at each follow-up time point - baseline score) / baseline score *100%.

Tabel 1 Participant timeline of data collection.

	Enrolment	Allocation/Surgery	Post-Surgery	Follow-up			
TIMEPOINT (weeks±1)	-1	0	1	4	12	24	48 (Close-out)
ENROLMENT :							
Eligibility screen	X						
Informed consent	X						
Medical history	X						
MRI scanning	X		X				
Allocation		X					
INTERVENTIONS :							
GPi-DBS surgery		X					
STN-DBS surgery		X					
DBS				X	X	X	X

ASSESSMENTS :							
Standardized video*	X			X	X	X	X
TWSTRS-disability	X			X	X	X	X
TWSTRS-pain	X			X	X	X	X
SF-36	X					X	X
HAMA	X					X	X
HAMD	X					X	X
MMSE	X					X	X
MoCA	X					X	X
Medication	X				X	X	X
Stimulation parameters				X	X	X	X
Adverse effects		X	X	X	X	X	X

* For assessment of TWSTRS-severity and Tsui scale

Sample size

The sample size is calculated based on one of the primary outcome —— the improvement rate of TWSTRS-severity subscore. According to the results of the latest meta-analysis comparing GPi-DBS with STN-DBS for CD treatment, the improvement rates (%) of TWSTRS-severity subscore at the same follow-up time (3 years) were 53.7±20.4 (GPi-DBS) and 39.3±26.4 (STN-DBS), respectively.[35] Based on the model of two independent sample T test, 41 patients for each group are required to reach a significant level of 5% (two-tailed) with 80% power. Assuming that 5% CD patients would be withdrawn from the trial and another 10% CD patients would be lost to follow-up, a total of 98 CD patients are required (49 patients for each group).

Randomization and blinding

Randomization is achieved through a central randomization system connected by web. For instance, having obtained the consent from an eligible patient or his/her family, a neurosurgeon of each center will submit the basic information of the patient to the online system, and then a unique random code and grouping information (GPi-DBS group or STN-DBS group) will be returned automatically. Only this neurosurgeon has access to the central randomization system.

Investigators (mostly neurosurgeons) are not blinded because of the nature of surgical intervention, but patients, scale raters, and data analysts are blinded. At the time of scales scoring and videos recording, each patient wears an operating cap so that scale raters are blinded to the condition of surgery (preoperatively or postoperatively). All standardized videos recorded for evaluation of TWSTRS-severity subscale and Tsui scale will be shuffled randomly and scored centrally by two experienced neurologists who do not know the grouping information and time points of follow-up. Furthermore, before data is transferred to data analysts for statistical analysis, data manager will mask the grouping information and set two groups as A and B instead. Only when the subjects are withdrawn would they be unblinded.

Data collection and management

The schematic chart for data collection is shown in table 1. Prior to the enrollment of the first patient, all investigators (including neurosurgeons, coordinators, scale raters, DBS programmers, data manager, etc) have to receive standardized training about the data collection and management. At baseline and each follow-up time point, all information (medical history, scales, videos, programming parameters, and adverse effects) will be transferred to a coordinator who will then fill

in the case report forms (CRFs). All items in CRFs have to be completed and any correction should be noted and explained. Eventually, two coordinators upload the standardized videos and input the information of CRFs into the electronic data capture (EDC) system —— Whole Course Management Service Platform (https://admin.demo.sdc.sinohealth.com/login).

Notably, the EDC system is embedded with a patient client that can be installed on patients' or their family's mobile phones, through which, investigators can push disease-related knowledge or questionnaires (for example, SF-36) to patients and conversely, patients can submit questionnaires and express their complaints to investigators at any time. Before each follow-up time point, patients will receive an alert from this client, thereby improving the follow-up compliance. For those withdrawn patients, the investigators also try to connect them and complete the 1-year follow-up.

During data collection, two data monitors will audit the contents of the CRFs to ensure data authenticity and accuracy. In addition, a data manager will review the EDC data online in real time and check the data consistency. Any data error or query existing, the data manager will send it back to the corresponding center where the investigators will check the original documents, answer the query, and update the data. At the end of the trial, the data manager will lock the EDC database and send the data to two data analysts for analysis.

All data files should be managed with great care and confidentiality. Only authorized investigators can log in the EDC system with password and any modification trace on the DEC platform will be preserved. Additionally, all original scale files and CRFs will be locked in a special cabinet and all video files will be stored in an encrypted folder.

Data monitor

Any adverse events during the study period should be documented in detail, including the information of event date, category, severity, treatment, and prognosis. If severe adverse events occur, the principal investigator must be notified within 24 hours.

Two study monitors who are independent of the implementation of this trial and have no competing interests will regularly visit the participating centers to inspect the protocol adherence, recruitment status, data collection, reporting of adverse events, and subject dropout rate. The monitoring results will be presented to the principal investigator and the local ethics committee. The interim analyses are unnecessary because plenty of previous studies have confirmed the safety of DBS surgery of both targets.[7, 10, 14, 16, 17, 29] Herein, this trial only concentrates on their potential differences.

Statistical analysis

Outcome statistics will be performed using cases with complete data, i.e., per protocol (PP) analyses. In addition, for the primary outcomes, an intention-to-treat (ITT) analysis (including all patients assigned in the trial) will also be performed with missing values imputed by multiple interpolation. Continuous variables will be presented as means ± standard deviations for normally distributed data or as medians (interquartile ranges) for skewed data. Categorical variables will be presented as frequencies or percentages. For difference analyses of baseline information, this study uses Wilcoxon rank-sum test for continuous variables and chi-square test or Fisher's exact test for categorical variables. Moreover, two-way ANOVA will be used to analyze the main effects (group or time) and the interaction effects. Within-group post hoc comparisons between different time points will be analyzed by paired T test or Wilcoxon signed-rank sum tests. Between-group comparisons at a certain time point will be analyzed using Wilcoxon rank-sum test. Factors associated with DBS efficacy, such as age at surgery and disease duration, will be included as covariates.[31, 34, 42] Finally, to explore predictors of DBS outcomes, this study use simple linear

regression first to screen variables relevant to the improvement rates of TWSTRS, and multiple linear regression second to identify independent variables.

A difference of $p < 0.05$ (two-tailed) is specified as statistically significant. SPSS 26 statistical software will be used for statistical analyses.

ETHICS AND DISSEMINATION

The PASTS-CD trial protocol has been approved by the Medical Ethics Committee of Chinese PLA General Hospital (S2022-613-01), which is also responsible for re-examining protocol modifications in the future, if any. Moreover, this trial has been registered on Clinicaltrials.gov (NCT05715138).

The investigators have to explain every surgical details to the patients or their family, and the informed consent form must be signed before allocation. For those patients with surgical sequelae, this study provides ancillary and post-trial care according to standard medical practice.

The investigators have access to the final results, which will be published in international peer-reviewed journals and shared in professional medical conferences. The raw data can be available from the corresponding author on reasonable request. Patients' information will be de-identified and videos will be mosaicked before exhibition.

DISCUSSION

To the best of our knowledge, the PASTS-CD study is the first prospective RCT study directly comparing the efficacy and safety of GPi-DBS and STN-DBS for refractory CD patients. The results of this trial will be a powerful guidance for neurosurgeons in selection of DBS target for CD patients. One notable advantage of this trial is that the primary outcomes are quantified by standardized videos centrally and blindly by two neurologists. The customized scheme of standardized video recording has been tested to suffice for the scoring of TWSTRS-severity subscale and Tsui scale. This design will eliminate the measurement bias from different scale raters of different centers and the interviewer bias from the subjectivity of scale raters. Another advantage is that this trial controls the confounding effect of electrode implantation accuracy, which is considered to be the most relevant factor to DBS efficacy.[43, 44] Due to the small size of the subcortical nuclei and the complex surrounding structures, a minor deviation from the target will bring about a significant disparity in DBS efficacy and adverse effects. Through measuring the distance between the sensorimotor subregion of target nuclei and the contacts of electrodes, the investigators exclude those subjects in which the volume of tissue activated (VTA) of DBS electrodes are speculated to show no or a low overlapping with the sensorimotor subregion of target nuclei. According to previous experiences[45, 46] and volume difference of the two targets, the cutoff distance is defined to be 3mm for STN-DBS group and 5mm for GPi-DBS group. This procedure also minimizing the influence of technical discrepancy of different neurosurgeons.

One possible limitation is that the neurosurgeons are not be blinded, but this is determined by the nature of surgical intervention. In fact, the main role of neurosurgeons is implanting the DBS electrodes into the predefined subregion of the two subcortical nuclei, and they do not participate in the subsequent scales scoring and DBS programming. As such, through controlling the accuracy of electrode position, the accompanying bias from the unblinded neurosurgeons will be significantly reduced. In addition, owing to the low incidence of CD, the investigators have to initiate a multicenter study to meet the requirement of sample size. Although multicenter studies may increase heterogeneity to some extent, it is believed that strict protocol implementation, coupled with systematic training and constant study monitoring, will help to minimize the biases and maximize

the reliability of results.

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Contributors

Study conception: MZQ and YXG. Initial study design: LB and XJP. Revision of study design and protocol: MZQ. statistical analysis: YHN. Study coordination: YXG. Drafting the manuscript: LB and XJP. All authors read and approved the final manuscript.

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Competing interests None declared.

Patients and public involvement Patients and the public are not involved in the design and implementation of this trial.

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Data availability statement Data are available upon reasonable request.

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Figure legend

Figure 1 Flow chart of the PASTS-CD study. GPi, globus pallidus internus; STN, subthalamic nucleus; DBS, deep brain stimulation.

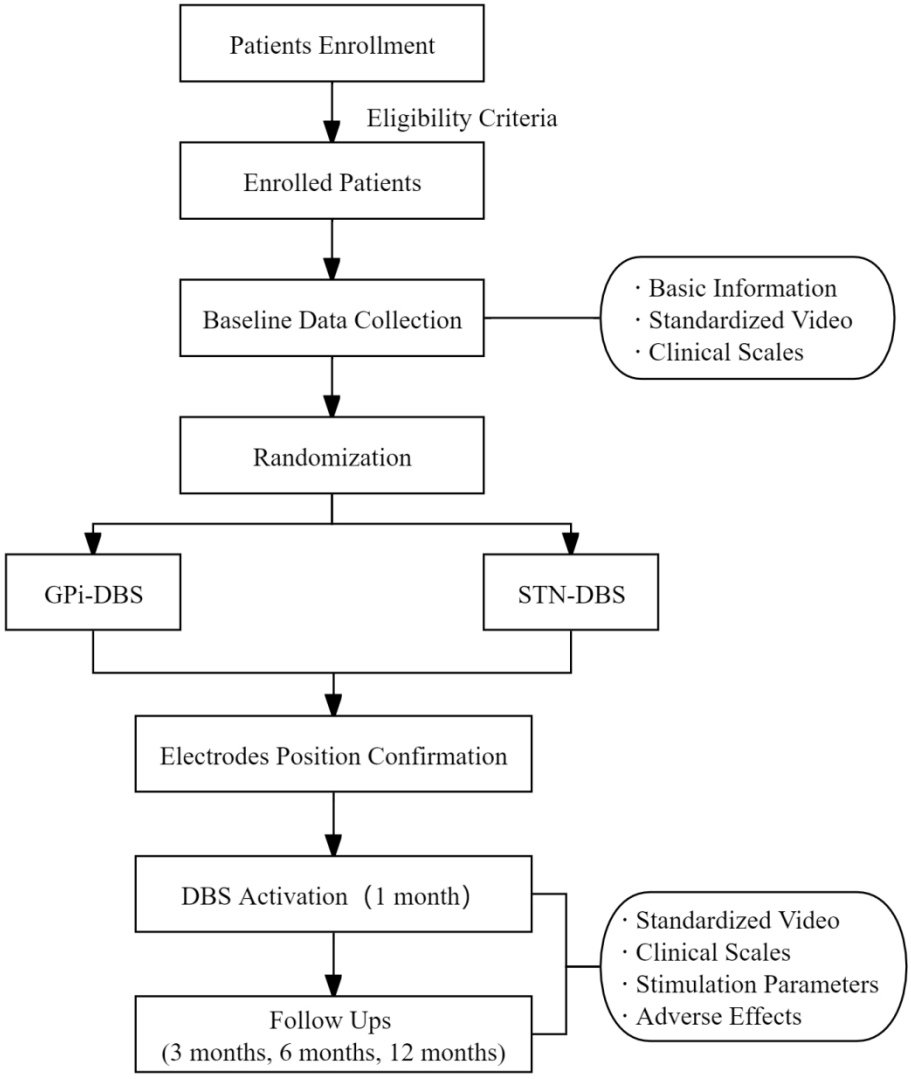

Figure 1 Flow chart of the PASTS-CD study. GPi, globus pallidus internus; STN, subthalamic nucleus; DBS, deep brain stimulation.

127x147mm (300 x 300 DPI)

Scheme of Standardized Video Recording

1. Seated position. (The patient wears a surgical cap with head, neck and shoulders on camera.)

① Eyes closed (20 seconds: 10 seconds recorded from the front and 10 seconds from the side).

Say to the patient, "Please sit down, close your eyes, and put your head where you feel most comfortable."

② Eyes open (10 seconds: 5 seconds recorded from the front and 5 seconds from the side).

Say to the patient, "Please sit down, open your eyes, and try to look straight ahead and keep your head in the middle."

③ Turn head right and turn head left (5 seconds each)

Say to the patient: "Look forward to the camera, turn your head to the right as far as you can, and then turn your head to the left as far as you can."

④ Head up and head down (5 seconds each)

Say to the patient: "Look forward to the camera, raise your head as high as you can, and then lower your head as low as you can."

⑤ Put the ear close to the right shoulder and then the left shoulder (5 seconds each).

Say to the patient, "Look forward to the camera. Now bring your right ear as close to your right shoulder as possible, and do not move your right shoulder."

Say to the patient, "Look forward to the camera. Now bring your left ear as close to your left shoulder as possible, and do not move your left shoulder."

⑥ Symptom persistence

Ask the patient, "If you divide your awake time during the day into four equal parts, how many parts do neck abnormalities take up?"

⑦ Symptom characteristics

Ask the patient, "Does each episode come on suddenly or gradually?"

⑧ Anterior view (Stop timing until the head is 10 degrees off center. Up to 60 seconds)

Say to the patient, "Please try to put your head in a straight position and look forward to the camera for one minute. Now start the clock."

⑨ Rest (10 seconds)

Say to the patient, "Rest for 10 seconds."

⑩ Anterior view (Stop timing until the head is 10 degrees off center. Up to 60 seconds)

Say to the patient, "Please do it again. Try to put your head in a straight position and look forward to the camera for one minute. Now start the clock."

⑪ Sensory tricks

Say to the patient, "Are there some movements or postures you can do to straighten your head? If so, try to do it."

2. Standing position (Show the whole body)

① Anterior view (5 seconds)

Say to the patient, "Please stand up and face the camera."

② Lateral view (5 seconds)

Say to the patient, "Please turn 90 degrees to the left (or right)."

3. Walking (10 seconds)

Say to the patient, "Please walk forward to the door and turn back."

Checklist

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title Page
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1, 8
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	Title Page
Funding	#4	Sources and types of financial, material, and other support	9
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	Title Page, 9
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a (no sponsor)
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a (no sponsor)
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	1-2

Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	1
Objectives	#7	Specific objectives or hypotheses	2-3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	3
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	3
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4-5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	4
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5-6

Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	3
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5-6, 6-7

Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	7-8
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	7-8
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	7-8
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a This trial sets two study mornitors (Page 8) instead of DMC.
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a No interim analyses (Page 8)
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	8

Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	8
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	9
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	8
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	8
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	8
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary materials
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

PAllidal versus SubThalamic deep brain Stimulation for Cervical Dystonia (PASTS-CD): study protocol for a multicenter randomized controlled trial

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Title: PAllidal versus SubThalamic deep brain Stimulation for Cervical Dystonia (PASTS-CD): study protocol for a multicenter randomized controlled trial

(Revised Version 1.0, 2023.07.26)

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ABSTRACT

Introduction Deep brain stimulation (DBS) has been validated as a safe and effective treatment for refractory cervical dystonia (CD). Globus pallidus internus (GPi) and subthalamic nucleus (STN) are the two main stimulating targets. However, there has been no prospective study to clarify which target is the better DBS candidate for CD. The objective of this trial is to compare directly the efficacy and safety of GPi-DBS and STN-DBS, thereby instructing the selection of DBS target in clinical practice.

Methods and analysis This multicenter, prospective, randomized, controlled study plans to enroll 98 refractory CD patients. Eligible CD patients will be randomly allocated to GPi-DBS group or STN-DBS group, with the DBS electrodes implanted into the posteroventral portion of GPi or the dorsolateral portion of STN, respectively. The primary outcome will be the improvement of symptomatic severity, measured by the changes in the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) severity subscale and the Tsui scale at 3 months, 6 months, and 12 months after surgery. The secondary outcomes include the improvement of the TWSTRS-disability subscale, TWSTRS-pain subscale, quality of life, mental and cognitive condition, as well as the differences in stimulation parameters and adverse effects. In addition, this study intends to identify certain predictors of DBS efficacy for CD.

Ethics and dissemination The trial has been approved by the Medical Ethics Committee of Chinese PLA General Hospital (S2022-613-01). The results of this study will be published in international peer-reviewed journals and shared in professional medical conferences.

Trial registration numbers NCT05715138

Key Words cervical dystonia, deep brain stimulation, globus pallidus internus, subthalamic nucleus.

ARTICLE SUMMARY

Strengths and limitations of this study

- The PASTS-CD study is the first randomized controlled study comparing the efficacy and safety of GPi-DBS and STN-DBS for cervical dystonia.
- The primary outcomes are evaluated blindly through randomly shuffled, de-identified, standardized videos to minimize potential biases.
- This trial uses the technique of imaging fusion to control the confounder of electrode position, which is deemed to be the major influence factor of DBS efficacy.
- One possible limitation is that investigators are not blinded because of the nature of the surgical intervention.

INTRODUCTION

Background and rationale

Cervical dystonia (CD), also known as spasmodic torticollis, is a type of focal dystonia, mainly manifesting as involuntary head turning or tilting, or holding a prolonged and twisted posture.[1, 2] CD limits the neck activity by involving one or a group of neck muscles and is often accompanied by pain and psychological disorders, seriously compromising patients' life quality.[2]

Medical treatment of CD is unsatisfactory. Oral medications are often ineffective or overshadowed by concomitant side effects.[2] Although most CD patients can be alleviated by injection of botulinum toxin, the remission is temporary so patients require multiple injections.[3] Moreover, 25% of patients do not respond to botulinum toxin, and 20%-40% of patients discontinued botulinum toxin treatment due to lack of benefit.[4, 5] Denervation and myotomy of the involved muscles is an effective surgery for CD once, but it becomes powerless in face of complicated cases.[6]

Deep brain stimulation (DBS) has been substantiated to be a safe and effective therapy for primary CD, even for those medically refractory cases.[7] The globus pallidus internus (GPi) was considered the preferred DBS target for various types of dystonia (including CD) with remarkable short-term and long-term efficacy.[7-16] In addition, stimulation of the subthalamic nucleus (STN) has drawn increasing attention in recent years with the superiorities of lower stimulation parameters requirement and shorter onset time. A series of studies have demonstrated that STN-DBS is a promising alternative to GPi-DBS, with a long-term symptomatic improvement rate ranging from 50% to 90%,[17-21] similar to and even higher than that of GPi-DBS. For studies focusing on CD only, both GPi-DBS[10, 22-27] and STN-DBS[17, 28, 29] show significant therapeutic effect. However, the question of which nucleus is the better DBS candidate for CD has not been clarified.

Previous comparisons of both targets were mainly about dystonia as a whole (including focal, segmental, and generalized dystonia). There was a prospective crossover study directly comparing the efficacy and safety of GPi-DBS and STN-DBS by implanting two sets of DBS electrodes for each dystonic patient and stimulating alternately one of them.[30, 31] The results seemed to favor STN-DBS at the 6-month follow-up,[30] but no significant between-group difference was found at the over ten-years follow-up.[31] Furthermore, another crossover study evaluated the effect of 24-hour stimulation of either STN or GPi for eight dystonic patients and also found no significant between-group difference.[32] Retrospectively, STN-DBS was proven to outperform GPi-DBS in terms of movement improvement at the 1-month follow-up, but this superiority disappeared later, and at the 12-month follow-up, GPi-DBS was more efficient than STN-DBS in treatment of axial symptoms.[33] Moreover, another meta-regression analysis indicated that STN-DBS, relative to GPi-DBS, is associated with a better outcome in the univariate regression model but not in the multivariate model.[34] However, these studies did not distinguish specific phenotypes (not focus on CD). Additionally, the prospective studies were degraded by their small sample size and the retrospective analyses yielded inconsistent results.

For CD specifically, there have been no prospective studies to compare GPi-DBS with STN-DBS. From a retrospective perspective, a meta-analysis comparatively analyzed the results of 13 relative studies, including 58 CD patients undergoing GPi-DBS and 28 CD patients undergoing STN-DBS.[35] They found that when the factor of follow-up time was not taken into account, the improvement rates of the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) subscores (severity, disability, and pain) were all significantly higher in the GPi-DBS group than that in the STN-DBS group, though the TWSTRS total score was not significantly different. Nevertheless, when the follow-up time was limited to three years, neither TWSTRS total score nor subscores showed a significantly between-group difference.[35] Similarly, another meta-analysis also failed to detect any significant difference — the improvement rates of the TWSTRS total score were 60.4% (GPi-DBS) and 56.6% (STN-DBS), respectively (p=0.936).[36] However, the two meta-analyses included low-quality studies and showed significant heterogeneity and publication bias. Surgeons still have confusion in the face of target selection before surgery. As such, a well-designed randomized controlled trial (RCT) is entailed to ascertain which one (STN or GPi) is the optimal DBS target for CD.

Objective

The PASTS-CD study aims to compare GPi-DBS with STN-DBS for drug-refractory CD in the following aspects: (1) improvement of dystonic symptoms (severity, disability, and pain), (2) improvement of life quality, mental status, and cognitive status, (3) stimulation parameters, (4)

adverse effects. In the end, the study intends to identify the potential factors that are associated with DBS efficacy in both groups.

METHODS AND ANALYSIS

Study design and setting

The PASTS-CD study is an investigator-initiated, multicenter, prospective, randomized, parallel-controlled equivalence clinical trial, following the rules of Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.[37] The method of minimization for randomization will be used to produce two paralleling arms with an allocation ratio of 1:1, both of which undergo the same procedures except for the difference in DBS target (GPi or STN). The flow chart of the trial is presented in figure 1. This study will be implemented from September 1, 2023 to November 30, 2026 in four tertiary hospitals in China. This study only incorporates hospitals that have been qualified in DBS surgery for more than 5 years with more than 20 DBS operations per year, and where DBS surgery-related complication rate is less than 5%. In addition, all investigators will go through a standardized training before trial initiation.

Participants

Recruitment

The investigators will post the recruitment announcement on each center's official website and WeChat account. CD Patients who are willing to participate in the trial will visit the dystonic outpatient of each center.

Inclusion criteria

(1) Diagnosed as idiopathic or hereditary isolated CD;
(2) Severe functional impairment;
(3) Oral medication and injection of botulinum toxin become ineffective (> 3 months since last injection), or refuse to adopt botulinum toxin injection;
(4) No secondary causes of CD;
(5) Age 18-80 years old;
(6) Normal neurological examination except for dystonia;
(7) Normal brain MRI;
(8) The subject or their family members can fully understand the trial and sign the informed consent;
(9) Good compliance and willingness to receive regular follow-ups.

Exclusion criteria

(1) Diagnosed as secondary CD;
(2) CD with obvious trunk/limb involvement, or Meige syndrome;
(3) History of severe mental disorders, dementia, or epilepsy;
(4) Previous dystonia surgery (pallidotomy, thalamotomy, DBS, etc);
(5) Accompanied by other neurological diseases (Parkinson's disease, essential tremor, multiple sclerosis, stroke, etc);
(6) The patient has or needs other implantable devices (cardiac pacemakers, defibrillators, cochlear implants, spinal cord stimulators, etc);
(7) Pregnant women or women who are waiting to become pregnant during the trial;
(8) Poor health condition.

Dropout or suspension of the trial

(1) Postoperative infection that requires removal of DBS electrodes;

(2) Severe displacement of DBS electrodes position from the predefined targets (> 3mm for STN-DBS group and > 5mm for GPi-DBS group);
(3) Occurrence of severe adverse events or other serious diseases that interfere with the efficacy assessment;
(4) Loss to follow up;
(5) Requests from patients to withdraw from the trial;

Interventions

Baseline evaluation

For each eligible patient, the basic information, medical history, disease characteristics, and medications will be recorded in the electronic medical record system in detail. Besides, physical examination, routine blood tests, and MRI scanning are assigned before surgery. Every patient will be videotaped as per a standardized scheme (see supplementary material) at least one day after drug withdrawal. These videos will be collected and transferred to two neurological raters who will complete the TWSTRS-severity subscale and Tsui scale blindly and separately at the end of the trial. Moreover, the TWSTRS-disability subscale, TWSTRS-pain subscale, 36-item Short Form General Health Survey (SF-36), Hamilton Anxiety Scale (HAMA), Hamilton Depression Scale (HAMD), Mini-Mental State Examination (MMSE), and Montreal Cognitive Assessment (MoCA) will also be completed before surgery. The timeline of data collection is shown in table 1. After signature of the informed consent form, candidate patients will be randomized into the GPi-DBS group or the STN-DBS group.

DBS surgery

Certain minor differences in surgical procedures are allowed among involved centers as long as the electrodes are placed safely and accurately, but some critical steps must keep in line with each other. Specifically, on the day of surgery, a stereotactic head frame is fixed on the patient's head, followed by a CT scan. The frame CT images and the preoperative MRI images (1.0 * 1.0 * 1.0 mm^3, no gap) will be fused in a surgical planning system, where the coordinates of the targets and trajectories are determined. DBS electrodes are implanted with the assistance of a stereotactic frame or neurosurgical robot under general anesthesia with bi-spectral index monitoring (BIS). After completion of burr holes, microelectrode recording (MER) is monitored intraoperatively to further assist the targeting of nuclei. The dosage of propofol should be reduced on recording, keeping the value of BIS fluctuating around 70, so as not to affect neuronal discharges.[38] An eligible firing pattern should be recorded as described by Robert, et al.[39] If not, the target should be adjusted or use two- or multiple-channel recording. Passive limb movements can be helpful to identify the sensorimotor subregion of the nuclei. Given that patients are under general anesthesia and their heads are immobilized by the frame, intraoperative macrostimulation can be omitted. Subsequently, according to the randomized allocation, the corresponding quadripolar electrodes will be implanted into posteroventral GPi (GPi-DBS group) or dorsolateral STN (STN-DBS group), bilaterally. The implanted electrodes can be selected from anyone of the following three manufacturers: Medtronic (Minneapolis, USA), PINS Medical (Beijing, China), and SceneRay (Suzhou, China). Of note, in light of the volume difference between the two nuclei, electrodes with contact intervals of 1.5mm are chosen for GPi-DBS, but 0.5mm for STN-DBS. Afterwards, inserted leads will be fixed at the burr hole site and an implantable pulse generator (IPG) will be connected and implanted at the right subclavicular area subcutaneously.

Electrode position confirmation

If possible, an intraoperative MRI scanning is strongly recommended to verify the implantation accuracy. Otherwise, a postoperative MRI or CT scanning is compulsory before discharge from hospitals. In order to exclude the effect of electrode position on the DBS efficacy, the intraopetative or postoperative images are fused with the preoperative images. If the deviating Euclidean distance between the lead tip and the predefined target exceeds 3mm (STN-DBS group) or 5mm (GPi-DBS group), the subject will be dropped out.

Follow-up

One month later, the DSB will be activated by a specialized DBS programmer in the outpatient department. To evaluate stimulation effects and adverse effects of both electrodes, all contacts will be screened in a monopolar mode with the voltage increasing gradually from 1V to 4V and pulse width and frequency kept at 60us and 130Hz. For those whose symptoms improve rapidly, the optimal parameters will be documented and used for chronic stimulation. For those who lack an acute improvement, the activated contact is identified based on the results of MER or the 3D reconstruction of the electrodes via the Lead DBS software (the contact closest to the posteroventral GPi or the dorsolateral STN), and the voltage is set at 25% below the threshold for causing a stimulation-related adverse effect. At the 3-month follow-up, a standardized video will be recorded and TWSTRS-disability and pain subscales are completed by a centrally-trained rater. At the 6-month and 12-month follow-ups, in addition to the standardized video and TWSTRS subscales, all the other scales (i.e. SF-36, HAMA, HAMD, MMSE, and MoCA) will also be evaluated (table 1). Of note, to focus on the effect of DBS and exclude the confounding effect of medication, botulinum toxin injection is forbidden during the follow-up period, and the patient should stop taking oral medication for one day before each evaluation. Furthermore, throughout the implementation of the trial, all adverse effects must be handled in safety and documented in detail, regardless of surgery-derived, device-related, or stimulation-induced events. Regular programming will also be performed at each follow-up to find the best parameters. The initial stimulating setting can be modulated at any time when the patients feel unsatisfactory about the symptom control or encounter a stimulation-induced adverse effect.

Outcome measurements

The primary outcomes are the changes (improvement rates) of the TWSTRS-severity subscale and the Tsui scale at 3 months, 6 months, and 12 months after surgery. The reason why these two scales are chosen as the primary outcomes is that both of them are obtained from standardized videos, while the TWSTRS disability and pain subscales can be acquired via questionnaires. The Tsui scale is a rational complement to the TWSTRS-severity subscale by adding the assessment of head tremor. The secondary outcomes are the changes (improvement rates) of the TWSTRS-disability subscale, TWSTRS-pain subscale, the difference of stimulation parameters and adverse effects at 3 months, 6 months, and 12 months after surgery, as well as the SF-36 questionnaire, HAMA scale, HAMD scale, MMSE scale, and MoCA scale at 6 months and 12 months after surgery. The improvement rate of each scale can be calculated by the following formula: (score at each follow-up time point - baseline score) / baseline score *100%. Stimulation parameters are mirrored by the total electrical energy delivered (TEED = voltage^2 * pulse width * frequency *1 second / impedance).[40] The higher the TEED, the shorter the battery life of the stimulator.

Table 1 Participant timeline of data collection.

	Enrolment	Allocation/Surgery	Post-Surgery	Follow-up

TIMEPOINT (weeks±1)	-1	0	1	4	12	24	48 (Close-out)
ENROLMENT :							
Eligibility screen	X						
Informed consent	X						
Medical history	X						
MRI scanning	X		X				
Allocation		X					
INTERVENTIONS :							
GPi-DBS surgery		X					
STN-DBS surgery		X					
DBS				X	X	X	X
ASSESSMENTS :							
Standardized video*	X				X	X	X
TWSTRS-disability	X				X	X	X
TWSTRS-pain	X				X	X	X
SF-36	X					X	X
HAMA	X					X	X
HAMD	X					X	X
MMSE	X					X	X
MoCA	X					X	X
Medication	X				X	X	X
Stimulation parameters				X	X	X	X
Adverse effects		X	X	X	X	X	X

* For assessment of TWSTRS-severity and Tsui scale

Sample size

The sample size is calculated based on one of the primary outcomes — the improvement rate of TWSTRS-severity subscore. According to the results of the latest meta-analysis comparing GPi-DBS with STN-DBS for CD treatment, the improvement rates (%) of TWSTRS-severity subscore at the same follow-up time (3 years) were 53.7±20.4 (GPi-DBS) and 39.3±26.4 (STN-DBS), respectively.[35] Based on the model of two independent sample T test, 41 patients for each group are required to reach a significant level of 5% (two-tailed) with 80% power. Assuming that 5% of CD patients would be withdrawn from the trial and another 10% of CD patients would be lost to follow-up, a total of 98 CD patients are required (49 patients for each group).

Randomization and blinding

Patients will be randomly assigned (1:1) to GPi-DBS group or STN-DBS group by using a bespoke web-based randomization sequence generated by the minimization method with a random component with gender (male or female), CD subtypes (phasic type or tonic type), and disease duration (< 3 years or ≥ 3 years) as factors of allocation adjustment. Randomization was stratified by participating centers. A specific neurosurgeon of each center who will participate in the DBS surgery submits the basic information of the patient to the online system, and then a unique random code and grouping information will be returned automatically. Only this neurosurgeon has access to the central randomization system.

Investigators (neurosurgeons) are not blinded because of the nature of the surgical intervention, but patients, scale raters, and data analysts are blinded. At the time of scale scoring and video recording, each patient wears an operating cap so that scale raters are blinded to the condition of surgery (preoperatively or postoperatively). All standardized videos recorded for evaluation of the TWSTRS-severity subscale and the Tsui scale will be shuffled randomly and scored twice centrally by two experienced neurologists who do not know the grouping information and time points of follow-up. The mean score values of the two neurologists will be documented and uploaded. Furthermore, before data is transferred to data analysts for statistical analysis, the data manager will mask the grouping information and set two groups as A and B instead. Only when the subjects are withdrawn would they be unblinded.

Data collection and management

The schematic chart for data collection is shown in table 1. Prior to the enrollment of the first patient, all investigators (including neurosurgeons, coordinators, scale raters, DBS programmers, data managers, etc) have to receive standardized training in data collection and management. At baseline and each follow-up time point, all information (medical history, scales, videos, programming parameters, and adverse effects) will be transferred to a coordinator who will then fill in the case report forms (CRFs). All items in CRFs have to be completed and any correction should be noted and explained. Eventually, two coordinators upload the standardized videos and input the information of CRFs into the electronic data capture (EDC) system — Whole Course Management Service Platform (https://admin.demo.sdc.sinohealth.com/login).

Notably, the EDC system is linked with a patient client that can be installed on patients' or their family's mobile phones, through which, investigators can push disease-related knowledge or questionnaires (for example, SF-36) to patients and conversely, patients can submit questionnaires and express their complaints to investigators at any time. Before each follow-up time point, patients will receive an alert from this client, thereby improving follow-up compliance.

During data collection, two data monitors will audit the contents of the CRFs to ensure data authenticity and accuracy. In addition, a data manager will review the EDC data online in real-time and check the data consistency. Any data error or query existing, the data manager will send it back to the corresponding center where the investigators will check the original documents, answer the query, and update the data. At the end of the trial, the data manager will lock the EDC database and send the data to two data analysts for analysis.

All data files should be managed with great care and confidentiality. Only authorized investigators can login the EDC system with a password and any modification trace on the DEC platform will be preserved. Additionally, all original scale files and CRFs will be locked in a special cabinet and all video files will be stored in an encrypted folder.

Data monitor

Any adverse events during the study period should be documented in detail, including the information of event date, category, severity, treatment, and prognosis. If severe adverse events occur, the principal investigator must be notified within 24 hours.

Two study monitors who are independent of the implementation of this trial and have no competing interests will regularly visit the participating centers to inspect the protocol adherence, recruitment status, data collection, reporting of adverse events, and subject dropout rate. The monitoring results will be presented to the principal investigator and the local ethics committee. The interim analyses

are unnecessary because plenty of previous studies have confirmed the safety of DBS surgery of both targets.[7, 10, 14, 16, 17, 29] Herein, this trial only concentrates on their potential differences.

Statistical analysis

Outcome statistics will be performed using cases with complete data, i.e., per protocol (PP) analyses. In addition, for the primary outcomes, an intention-to-treat (ITT) analysis (including all patients assigned in the trial) will also be performed with missing values imputed by multiple interpolations. Continuous variables will be presented as means ± standard deviations for normally distributed data or as medians (interquartile ranges) for skewed data. Categorical variables will be presented as frequencies or percentages. For difference analyses of baseline information, this study uses the Wilcoxon rank-sum test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. Moreover, two-way ANOVA will be used to analyze the main effects (group or time) and the interaction effects. Within-group post hoc comparisons between different time points will be analyzed by paired T test or Wilcoxon signed-rank sum tests. Between-group comparisons at a certain time point will be analyzed using the Wilcoxon rank-sum test. Factors associated with DBS efficacy, such as gender, age at surgery, and disease duration, will be included as covariates.[31, 34, 41] Of note, when analyzing the adverse effects, those patients who have been withdrawn due to severe adverse effects should be included. Finally, to explore predictors of DBS outcomes, this study uses simple linear regression first to screen variables relevant to the improvement rates of TWSTRS, and multiple linear regression second to identify independent variables.

A difference of $p < 0.05$ (two-tailed) is specified as statistically significant. SPSS 26 statistical software will be used for statistical analyses.

ETHICS AND DISSEMINATION

The PASTS-CD trial protocol has been approved by the Medical Ethics Committee of Chinese PLA General Hospital (S2022-613-01), which is also responsible for re-examining protocol modifications in the future, if any. Moreover, this trial has been registered on Clinicaltrials.gov (NCT05715138).

The investigators have to explain the objectives of this trial and every surgical detail to the patients or their families, and the informed consent form must be signed before allocation. For those patients with surgical sequelae, this study provides ancillary and post-trial care according to standard medical practice.

The investigators have access to the final results, which will be published in international peer-reviewed journals and shared in professional medical conferences. The raw data can be available from the corresponding author upon reasonable request. Patients' information will be de-identified and videos will be mosaicked before exhibition.

DISCUSSION

To the best of our knowledge, the PASTS-CD study is the first prospective RCT study directly comparing the efficacy and safety of GPi-DBS and STN-DBS for refractory CD patients. The results of this trial will be a powerful guide for neurosurgeons in the selection of DBS targets for CD patients.

One notable advantage of this trial is that the primary outcomes are quantified by standardized videos centrally and blindly by two neurologists. The customized scheme of standardized video recording has been tested to suffice for the scoring of the TWSTRS-severity subscale and Tsui scale. This design will eliminate the measurement bias from different scale raters of different centers and

the interviewer bias from the subjectivity of scale raters. Another advantage is that this trial controls the confounding effect of electrode implantation accuracy, which is considered to be the most relevant factor to DBS efficacy.[42, 43] Due to the small size of the subcortical nuclei and the complex surrounding structures, a minor deviation from the target will bring about a significant disparity in DBS efficacy and adverse effects. Through measuring the distance between the sensorimotor subregion of target nuclei and the contacts of electrodes, the investigators exclude those subjects in which the volume of tissue activated (VTA) of DBS electrodes is speculated to show no or a low overlapping with the sensorimotor subregion of target nuclei. According to previous experiences[44, 45] and the volume difference between the two targets, the cutoff distance is defined to be 3mm for the STN-DBS group and 5mm for the GPi-DBS group. This procedure also minimizes the influence of technical discrepancy of different neurosurgeons.

One possible limitation is that the neurosurgeons are not blinded, but this is determined by the nature of the surgical intervention. In fact, the main role of neurosurgeons is implanting the DBS electrodes into the predefined subregion of the two subcortical nuclei, and they do not participate in the subsequent scales scoring and DBS programming. As such, by controlling the accuracy of electrode position, the accompanying bias from the unblinded neurosurgeons will be significantly reduced. In addition, owing to the low incidence of CD, the investigators have to initiate a multicenter study to meet the requirement of sample size. Although multicenter studies may increase heterogeneity to some extent, it is believed that strict protocol implementation, coupled with systematic training and constant study monitoring, will help to minimize the biases and maximize the reliability of results.

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Contributors

Study conception: MZQ and YXG. Initial study design: LB and XJP. Revision of study design and protocol: MZQ. statistical analysis: YHN. Study coordination: YXG. Drafting the manuscript: LB and XJP. All authors read and approved the final manuscript.

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Competing interests None declared.

Patients and public involvement Patients and the public are not involved in the design and implementation of this trial.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer-reviewed.

Data availability statement Data are available upon reasonable request.

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postoperative motor outcome. Mov Disord 2012;27:874-9.
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Figure legend

Figure 1 Flow chart of the PASTS-CD study. GPi, globus pallidus internus; STN, subthalamic nucleus; DBS, deep brain stimulation.

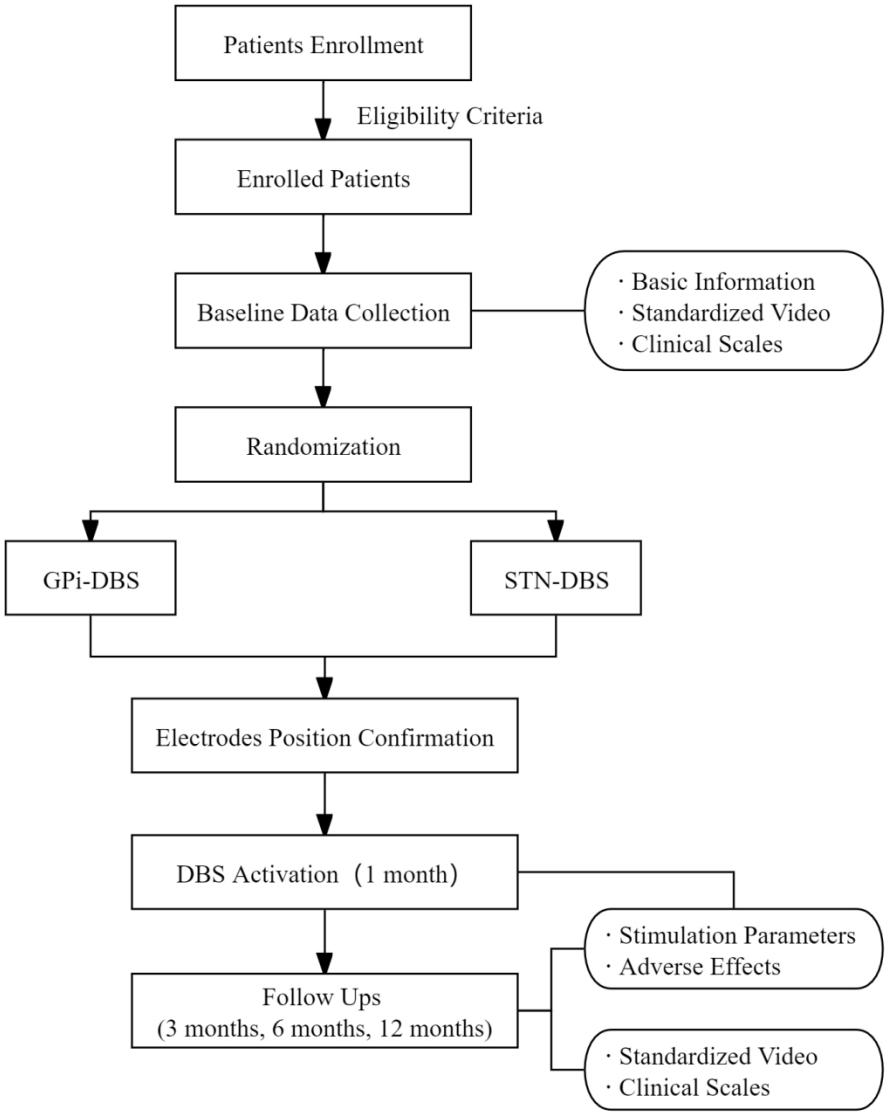

Figure 1 Flow chart of the PASTS-CD study. GPi, globus pallidus internus; STN, subthalamic nucleus; DBS, deep brain stimulation.

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Checklist

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title Page
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1, 8
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	Title Page
Funding	#4	Sources and types of financial, material, and other support	9
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	Title Page, 9
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a (no sponsor)
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a (no sponsor)
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	1-2

Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	1
Objectives	#7	Specific objectives or hypotheses	2-3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	3
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	3
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4-5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	4
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5-6

Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	3
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5-6, 6-7

Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a This trial sets two study mornitors (Page 7-8) instead of DMC.
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a No interim analyses (Page 7-8)
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	8

Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	8
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	9
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	8
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	8
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	8
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary materials
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

Scheme of Standardized Video Recording

1. Seated position. (The patient wears a surgical cap with head, neck and shoulders on camera.)

① Eyes closed (20 seconds: 10 seconds recorded from the front and 10 seconds from the side).

Say to the patient, "Please sit down, close your eyes, and put your head where you feel most comfortable."

② Eyes open (10 seconds: 5 seconds recorded from the front and 5 seconds from the side).

Say to the patient, "Please sit down, open your eyes, and try to look straight ahead and keep your head in the middle."

③ Turn head right and turn head left (5 seconds each)

Say to the patient: "Look forward to the camera, turn your head to the right as far as you can, and then turn your head to the left as far as you can."

④ Head up and head down (5 seconds each)

Say to the patient: "Look forward to the camera, raise your head as high as you can, and then lower your head as low as you can."

⑤ Put the ear close to the right shoulder and then the left shoulder (5 seconds each).

Say to the patient, "Look forward to the camera. Now bring your right ear as close to your right shoulder as possible, and do not move your right shoulder."

Say to the patient, "Look forward to the camera. Now bring your left ear as close to your left shoulder as possible, and do not move your left shoulder."

⑥ Symptom persistence

Ask the patient, "If you divide your awake time during the day into four equal parts, how many parts do neck abnormalities take up?"

⑦ Symptom characteristics

Ask the patient, "Does each episode come on suddenly or gradually?"

⑧ Anterior view (Stop timing until the head is 10 degrees off center. Up to 60 seconds)

Say to the patient, "Please try to put your head in a straight position and look forward to the camera for one minute. Now start the clock."

⑨ Rest (10 seconds)

Say to the patient, "Rest for 10 seconds."

⑩ Anterior view (Stop timing until the head is 10 degrees off center. Up to 60 seconds)

Say to the patient, "Please do it again. Try to put your head in a straight position and look forward to the camera for one minute. Now start the clock."

⑪ Sensory tricks

Say to the patient, "Are there some movements or postures you can do to straighten your head? If so, try to do it."

2. Standing position (Show the whole body)

① Anterior view (5 seconds)

Say to the patient, "Please stand up and face the camera."

② Lateral view (5 seconds)

Say to the patient, "Please turn 90 degrees to the left (or right)."

3. Walking (10 seconds)

Say to the patient, "Please walk forward to the door and turn back."

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PAllidal versus SubThalamic deep brain Stimulation for Cervical Dystonia (PASTS-CD): study protocol for a multicenter randomized controlled trial

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Title: PAllidal versus SubThalamic deep brain Stimulation for Cervical Dystonia (PASTS-CD): study protocol for a multicenter randomized controlled trial

(Revised Version 3.0, 2023.08.22)

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ABSTRACT

Introduction Deep brain stimulation (DBS) has been validated as a safe and effective treatment for refractory cervical dystonia (CD). Globus pallidus internus (GPi) and subthalamic nucleus (STN) are the two main stimulating targets. However, there has been no prospective study to clarify which target is the better DBS candidate for CD. The objective of this trial is to compare directly the efficacy and safety of GPi-DBS and STN-DBS, thereby instructing the selection of DBS target in clinical practice.

Methods and analysis This multicenter, prospective, randomized, controlled study plans to enroll 98 refractory CD patients. Eligible CD patients will be randomly allocated to GPi-DBS group or STN-DBS group, with the DBS electrodes implanted into the posteroventral portion of GPi or the dorsolateral portion of STN, respectively. The primary outcome will be the improvement of symptomatic severity, measured by the changes in the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) severity subscale and the Tsui scale at 3 months, 6 months, and 12 months after surgery. The secondary outcomes include the improvement of the TWSTRS-disability subscale, TWSTRS-pain subscale, quality of life, mental and cognitive condition, as well as the differences in stimulation parameters and adverse effects. In addition, this study intends to identify certain predictors of DBS efficacy for CD.

Ethics and dissemination The trial has been approved by the Medical Ethics Committee of Chinese PLA General Hospital (S2022-613-01). The results of this study will be published in international peer-reviewed journals and shared in professional medical conferences.

Trial registration numbers NCT05715138

Key Words cervical dystonia, deep brain stimulation, globus pallidus internus, subthalamic nucleus.

ARTICLE SUMMARY

Strengths and limitations of this study

The PASTS-CD study is the first randomized controlled study comparing the efficacy and safety of GPi-DBS and STN-DBS for cervical dystonia.

The primary outcomes are evaluated blindly through randomly shuffled, de-identified, standardized videos to minimize potential biases.

This trial uses the technique of imaging fusion to control the confounder of electrode position, which is deemed to be the major influence factor of DBS efficacy.

One possible limitation is that investigators are not blinded because of the nature of the surgical intervention.

INTRODUCTION

Background and rationale

Cervical dystonia (CD), also known as spasmodic torticollis, is a type of focal dystonia, mainly manifesting as involuntary head turning or tilting, or holding a prolonged and twisted posture.[1, 2] CD limits the neck activity by involving one or a group of neck muscles and is often accompanied by pain and psychological disorders, seriously compromising patients' life quality.[2]

Medical treatment of CD is unsatisfactory. Oral medications are often ineffective or overshadowed by concomitant side effects.[2] Although most CD patients can be alleviated by injection of botulinum toxin, the remission is temporary so patients require multiple injections.[3] Moreover, 25% of patients do not respond to botulinum toxin, and 20%-40% of patients discontinued botulinum toxin treatment due to lack of benefit.[4, 5] Denervation and myotomy of the involved muscles is an effective surgery

for CD once, but it becomes powerless in face of complicated cases.[6]

Deep brain stimulation (DBS) has been substantiated to be a safe and effective therapy for primary CD, even for those medically refractory cases.[7] The globus pallidus internus (GPi) was considered the preferred DBS target for various types of dystonia (including CD) with remarkable short-term and long-term efficacy.[7-16] In addition, stimulation of the subthalamic nucleus (STN) has drawn increasing attention in recent years with the superiorities of lower stimulation parameters requirement and shorter onset time. A series of studies have demonstrated that STN-DBS is a promising alternative to GPi-DBS, with a long-term symptomatic improvement rate ranging from 50% to 90%,[17-21] similar to and even higher than that of GPi-DBS. For studies focusing on CD only, both GPi-DBS[10, 22-27] and STN-DBS[17, 28, 29] show significant therapeutic effect. However, the question of which nucleus is the better DBS candidate for CD has not been clarified.

Previous comparisons of both targets were mainly about dystonia as a whole (including focal, segmental, and generalized dystonia). There was a prospective crossover study directly comparing the efficacy and safety of GPi-DBS and STN-DBS by implanting two sets of DBS electrodes for each dystonic patient and stimulating alternately one of them.[30, 31] The results seemed to favor STN-DBS at the 6-month follow-up,[30] but no significant between-group difference was found at the over ten-years follow-up.[31] Furthermore, another crossover study evaluated the effect of 24-hour stimulation of either STN or GPi for eight dystonic patients and also found no significant between-group difference.[32] Retrospectively, STN-DBS was proven to outperform GPi-DBS in terms of movement improvement at the 1-month follow-up, but this superiority disappeared later, and at the 12-month follow-up, GPi-DBS was more efficient than STN-DBS in treatment of axial symptoms.[33] Moreover, another meta-regression analysis indicated that STN-DBS, relative to GPi-DBS, is associated with a better outcome in the univariate regression model but not in the multivariate model.[34] However, these studies did not distinguish specific phenotypes (not focus on CD). Additionally, the prospective studies were degraded by their small sample size and the retrospective analyses yielded inconsistent results.

For CD specifically, there have been no prospective studies to compare GPi-DBS with STN-DBS. From a retrospective perspective, a meta-analysis comparatively analyzed the results of 13 relative studies, including 58 CD patients undergoing GPi-DBS and 28 CD patients undergoing STN-DBS.[35] They found that when the factor of follow-up time was not taken into account, the improvement rates of the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) subscores (severity, disability, and pain) were all significantly higher in the GPi-DBS group than that in the STN-DBS group, though the TWSTRS total score was not significantly different. Nevertheless, when the follow-up time was limited to three years, neither TWSTRS total score nor subscores showed a significantly between-group difference.[35] Similarly, another meta-analysis also failed to detect any significant difference — the improvement rates of the TWSTRS total score were 60.4% (GPi-DBS) and 56.6% (STN-DBS), respectively (p=0.936).[36] However, the two meta-analyses included low-quality studies and showed significant heterogeneity and publication bias. Surgeons still have confusion in the face of target selection before surgery. As such, a well-designed randomized controlled trial (RCT) is entailed to ascertain which one (STN or GPi) is the optimal DBS target for CD.

Objective

The PASTS-CD study aims to compare GPi-DBS with STN-DBS for drug-refractory CD in the

following aspects: (1) improvement of dystonic symptoms (severity, disability, and pain), (2) improvement of life quality, mental status, and cognitive status, (3) stimulation parameters, (4) adverse effects. In the end, the study intends to identify the potential factors that are associated with DBS efficacy in both groups.

METHODS AND ANALYSIS

Study design and setting

The PASTS-CD study is an investigator-initiated, multicenter, prospective, randomized, parallel-controlled equivalence clinical trial, following the rules of Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.[37] The method of minimization for randomization will be used to produce two paralleling arms with an allocation ratio of 1:1, both of which undergo the same procedures except for the difference in DBS target (GPi or STN). The flow chart of the trial is presented in figure 1. This study will be implemented from September 1, 2023 to November 30, 2026 in four tertiary hospitals in China. This study only incorporates hospitals that have been qualified in DBS surgery for more than 5 years with more than 20 DBS operations per year, and where DBS surgery-related complication rate is less than 5%. In addition, all investigators will go through a standardized training before trial initiation.

Participants

Recruitment

The investigators will post the recruitment announcement on each center's official website and WeChat account. CD Patients who are willing to participate in the trial will visit the dystonic outpatient of each center.

Inclusion criteria

(1) Diagnosed as idiopathic or hereditary isolated CD;
(2) Severe functional impairment;
(3) Oral medication and injection of botulinum toxin become ineffective after at least two attempts (> 6 months since last injection);
(4) No secondary causes of CD;
(5) Age 18-80 years old;
(6) Normal neurological examination except for dystonia;
(7) Normal brain MRI;
(8) The subject or their family members can fully understand the trial and sign the informed consent;
(9) Good compliance and willingness to receive regular follow-ups.

Exclusion criteria

(1) Diagnosed as secondary CD;
(2) CD with obvious trunk/limb involvement, or Meige syndrome;
(3) History of severe mental disorders, dementia, or epilepsy;
(4) Previous dystonia surgery (pallidotomy, thalamotomy, DBS, etc);
(5) Accompanied by other neurological diseases (Parkinson's disease, essential tremor, multiple sclerosis, stroke, etc);
(6) The patient has or needs other implantable devices (cardiac pacemakers, defibrillators, cochlear implants, spinal cord stimulators, etc);

(7) Pregnant women or women who are waiting to become pregnant during the trial;
(8) Poor health condition.

Dropout or suspension of the trial

(1) Postoperative infection that requires removal of DBS electrodes;
(2) Severe displacement of DBS electrodes position from the predefined targets (> 3mm for STN-DBS group and > 5mm for GPi-DBS group);
(3) Occurrence of severe adverse events or other serious diseases that interfere with the efficacy assessment;
(4) Loss to follow up;
(5) Requests from patients to withdraw from the trial;

Interventions

Baseline evaluation

For each eligible patient, the basic information, medical history, disease characteristics, and medications (especially the time and frequency of botulinum toxin injection) will be recorded in the electronic medical record system in detail. Besides, physical examination, routine blood tests, and MRI scanning are assigned before surgery. Every patient will be videotaped as per a standardized scheme (see supplementary material) without drug withdrawal. These videos will be collected and transferred to two neurological raters who will complete the TWSTRS-severity subscale and Tsui scale blindly and separately at the end of the trial. Moreover, the TWSTRS-disability subscale, TWSTRS-pain subscale, 36-item Short Form General Health Survey (SF-36), Hamilton Anxiety Scale (HAMA), Hamilton Depression Scale (HAMD), Mini-Mental State Examination (MMSE), and Montreal Cognitive Assessment (MoCA) will also be completed before surgery. The timeline of data collection is shown in table 1. After signature of the informed consent form, candidate patients will be randomized into the GPi-DBS group or the STN-DBS group.

DBS surgery

Certain minor differences in surgical procedures are allowed among involved centers as long as the electrodes are placed safely and accurately, but some critical steps must keep in line with each other. Specifically, on the day of surgery, a stereotactic head frame is fixed on the patient's head, followed by a CT scan. The frame CT images and the preoperative MRI images (1.0 * 1.0 * 1.0 mm^3, no gap) will be fused in a surgical planning system, where the coordinates of the targets and trajectories are determined. DBS electrodes are implanted with the assistance of a stereotactic frame or neurosurgical robot under general anesthesia with bi-spectral index monitoring (BIS). After completion of burr holes, microelectrode recording (MER) is monitored intraoperatively to further assist the targeting of nuclei. The dosage of propofol should be reduced on recording, keeping the value of BIS fluctuating around 70, so as not to affect neuronal discharges.[38] An eligible firing pattern should be recorded as described by Robert, et al.[39] If not, the target should be adjusted or use two- or multiple-channel recording. Passive limb movements can be helpful to identify the sensorimotor subregion of the nuclei. Given that patients are under general anesthesia and their heads are immobilized by the frame, intraoperative macrostimulation can be omitted. Subsequently, according to the randomized allocation, the corresponding quadripolar electrodes will be implanted into posteroventral GPi (GPi-DBS group) or dorsolateral STN (STN-DBS group), bilaterally. The implanted electrodes can be selected from anyone

of the following three manufacturers: Medtronic (Minneapolis, USA), PINS Medical (Beijing, China), and SceneRay (Suzhou, China). Of note, in light of the volume difference between the two nuclei, electrodes with contact intervals of 1.5mm are chosen for GPi-DBS, but 0.5mm for STN-DBS. Afterwards, inserted leads will be fixed at the burr hole site and an implantable pulse generator (IPG) will be connected and implanted at the right subclavicular area subcutaneously.

Electrode position confirmation

If possible, an intraoperative MRI scanning is strongly recommended to verify the implantation accuracy. Otherwise, a postoperative MRI or CT scanning is compulsory before discharge from hospitals. In order to exclude the effect of electrode position on the DBS efficacy, the intraopetative or postoperative images are fused with the preoperative images. If the deviating Euclidean distance between the lead tip and the predefined target exceeds 3mm (STN-DBS group) or 5mm (GPi-DBS group), the subject will be dropped out.

Follow-up

One month later, the DSB will be activated by a specialized DBS programmer in the outpatient department. To evaluate stimulation effects and adverse effects of both electrodes, all contacts will be screened in a monopolar mode with the voltage increasing gradually from 1V to 4V and pulse width and frequency kept at 60us and 130Hz. For those whose symptoms improve rapidly, the optimal parameters will be documented and used for chronic stimulation. For those who lack an acute improvement, the activated contact is identified based on the results of MER or the 3D reconstruction of the electrodes via the Lead DBS software (the contact closest to the posteroventral GPi or the dorsolateral STN), and the voltage is set at 25% below the threshold for causing a stimulation-related adverse effect. At the 3-month follow-up, a standardized video will be recorded and TWSTRS-disability and pain subscales are completed by a centrally-trained rater. At the 6-month and 12-month follow-ups, in addition to the standardized video and TWSTRS subscales, all the other scales (i.e. SF-36, HAMA, HAMD, MMSE, and MoCA) will also be evaluated (table 1). Of note, to focus on the effect of DBS and exclude the confounding effect of medication, botulinum toxin injection is forbidden during the follow-up period, and in a week leading up to each evaluation, the patient should take the same oral drugs as before surgery. Furthermore, throughout the implementation of the trial, all adverse effects must be handled in safety and documented in detail, regardless of surgery-derived, device-related, or stimulation-induced events. Regular programming will also be performed at each follow-up to find the best parameters. The initial stimulating setting can be modulated at any time when the patients feel unsatisfactory about the symptom control or encounter a stimulation-induced adverse effect.

Outcome measurements

The primary outcomes are the changes (improvement rates) of the TWSTRS-severity subscale and the Tsui scale at 3 months, 6 months, and 12 months after surgery. The reason why these two scales are chosen as the primary outcomes is that both of them are obtained from standardized videos, while the TWSTRS disability and pain subscales can be acquired via questionnaires. The Tsui scale is a rational complement to the TWSTRS-severity subscale by adding the assessment of head tremor.

The secondary outcomes are the changes (improvement rates) of the TWSTRS-disability subscale, TWSTRS-pain subscale, the difference of stimulation parameters and adverse effects at 3 months, 6 months, and 12 months after surgery, as well as the SF-36 questionnaire, HAMA scale, HAMD scale,

MMSE scale, and MoCA scale at 6 months and 12 months after surgery. The improvement rate of each scale can be calculated by the following formula: (score at each follow-up time point - baseline score) / baseline score *100%. Stimulation parameters are mirrored by the total electrical energy delivered (TEED = voltage^2 * pulse width * frequency *1 second / impedance).[40] The higher the TEED, the shorter the battery life of the stimulator. To quantify the adverse effects, the Timed Up and Go (TUG) test is used to evaluate the severity of bradykinesia (the most common adverse effect for GPi-DBS) and the Abnormal Involuntary Movement scale (AIMs) is used to estimate the severity of dyskinesia (the most common adverse effect for STN-DBS).

Table 1 Participant timeline of data collection.

	Enrolment	Allocation/Surgery	Post-Surgery	Follow-up			
TIMEPOINT (weeks±1)	-1	0	1	4	12	24	48 (Close-out)
ENROLMENT :							
Eligibility screen	X						
Informed consent	X						
Medical history	X						
MRI scanning	X		X				
Allocation		X					
INTERVENTIONS :							
GPi-DBS surgery		X					
STN-DBS surgery		X					
DBS				X	X	X	X
ASSESSMENTS :							
Standardized video*	X				X	X	X
TWSTRS-disability	X				X	X	X
TWSTRS-pain	X				X	X	X
SF-36	X					X	X
HAMA	X					X	X
HAMD	X					X	X
MMSE	X					X	X
MoCA	X					X	X
Medication	X				X	X	X
Stimulation parameters				X	X	X	X
Adverse effects		X	X	X	X	X	X

* For assessment of TWSTRS-severity and Tsui scale

Sample size

The sample size is calculated based on one of the primary outcomes — the improvement rate of TWSTRS-severity subscore. According to the results of the latest meta-analysis comparing GPi-DBS with STN-DBS for CD treatment, the improvement rates (%) of TWSTRS-severity subscore at the same

follow-up time (3 years) were 53.7±20.4 (GPi-DBS) and 39.3±26.4 (STN-DBS), respectively.[35] Based on the model of two independent sample T test, 41 patients for each group are required to reach a significant level of 5% (two-tailed) with 80% power. Assuming that 5% of CD patients would be withdrawn from the trial and another 10% of CD patients would be lost to follow-up, a total of 98 CD patients are required (49 patients for each group).

Randomization and blinding

Patients will be randomly assigned (1:1) to GPi-DBS group or STN-DBS group by using a bespoke web-based randomization sequence generated by the minimization method with a random component with gender (male or female), CD subtypes (phasic type or tonic type), and disease duration (< 3 years or ≥ 3 years) as factors of allocation adjustment. Randomization was stratified by participating centers.

A specific neurosurgeon of each center who will participate in the DBS surgery submits the basic information of the patient to the online system, and then a unique random code and grouping information will be returned automatically. Only this neurosurgeon has access to the central randomization system. Investigators (neurosurgeons) are not blinded because of the nature of the surgical intervention, but patients, scale raters, and data analysts are blinded. At the time of scale scoring and video recording, each patient wears an operating cap so that scale raters are blinded to the condition of surgery (preoperatively or postoperatively). All standardized videos recorded for evaluation of the TWSTRS-severity subscale and the Tsui scale will be shuffled randomly and scored twice centrally by two experienced neurologists who do not know the grouping information and time points of follow-up. The mean score values of the two neurologists will be documented and uploaded. Furthermore, before data is transferred to data analysts for statistical analysis, the data manager will mask the grouping information and set two groups as A and B instead. Only when the subjects are withdrawn would they be unblinded.

Data collection and management

The schematic chart for data collection is shown in table 1. Prior to the enrollment of the first patient, all investigators (including neurosurgeons, coordinators, scale raters, DBS programmers, data managers, etc) have to receive standardized training in data collection and management. At baseline and each follow-up time point, all information (medical history, scales, videos, programming parameters, and adverse effects) will be transferred to a coordinator who will then fill in the case report forms (CRFs). All items in CRFs have to be completed and any correction should be noted and explained. Eventually, two coordinators upload the standardized videos and input the information of CRFs into the electronic data capture (EDC) system — Whole Course Management Service Platform (https://admin.demo.sdc.sinohealth.com/login).

Notably, the EDC system is linked with a patient client that can be installed on patients' or their family's mobile phones, through which, investigators can push disease-related knowledge or questionnaires (for example, SF-36) to patients and conversely, patients can submit questionnaires and express their complaints to investigators at any time. Before each follow-up time point, patients will receive an alert from this client, thereby improving follow-up compliance.

During data collection, two data monitors will audit the contents of the CRFs to ensure data authenticity and accuracy. In addition, a data manager will review the EDC data online in real-time and check the

data consistency. Any data error or query existing, the data manager will send it back to the corresponding center where the investigators will check the original documents, answer the query, and update the data. At the end of the trial, the data manager will lock the EDC database and send the data to two data analysts for analysis.

All data files should be managed with great care and confidentiality. Only authorized investigators can login the EDC system with a password and any modification trace on the DEC platform will be preserved. Additionally, all original scale files and CRFs will be locked in a special cabinet and all video files will be stored in an encrypted folder.

Data monitor

Any adverse events during the study period should be documented in detail, including the information of event date, category, severity, treatment, and prognosis. If severe adverse events occur, the principal investigator must be notified within 24 hours.

Two study monitors who are independent of the implementation of this trial and have no competing interests will regularly visit the participating centers to inspect the protocol adherence, recruitment status, data collection, reporting of adverse events, and subject dropout rate. The monitoring results will be presented to the principal investigator and the local ethics committee. The interim analyses are unnecessary because plenty of previous studies have confirmed the safety of DBS surgery of both targets.[7, 10, 14, 16, 17, 29] Herein, this trial only concentrates on their potential differences.

Statistical analysis

Outcome statistics will be performed using cases with complete data, i.e., per protocol (PP) analyses. In addition, for the primary outcomes, an intention-to-treat (ITT) analysis (including all patients assigned in the trial) will also be performed with missing values imputed by multiple interpolations.

Continuous variables will be presented as means ± standard deviations for normally distributed data or as medians (interquartile ranges) for skewed data. Categorical variables will be presented as frequencies or percentages. For difference analyses of baseline information, this study uses the Wilcoxon rank-sum test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. Moreover, two-way ANOVA will be used to analyze the main effects (group or time) and the interaction effects. Within-group post hoc comparisons between different time points will be analyzed by paired T test or Wilcoxon signed-rank sum tests. Between-group comparisons at a certain time point will be analyzed using the Wilcoxon rank-sum test. Factors associated with DBS efficacy, such as gender, age at surgery, and disease duration, will be included as covariates.[31, 34, 41] Of note, when analyzing the adverse effects, those patients who have been withdrawn due to severe adverse effects should be included. Finally, to explore predictors of DBS outcomes, this study uses simple linear regression first to screen variables relevant to the improvement rates of TWSTRS, and multiple linear regression second to identify independent variables.

A difference of $p < 0.05$ (two-tailed) is specified as statistically significant. SPSS 26 statistical software will be used for statistical analyses.

Patients and public involvement

Patients and the public are not involved in the design and implementation of this trial.

ETHICS AND DISSEMINATION

The PASTS-CD trial protocol has been approved by the Medical Ethics Committee of Chinese PLA

General Hospital (S2022-613-01), which is also responsible for re-examining protocol modifications in the future, if any. Moreover, this trial has been registered on Clinicaltrials.gov (NCT05715138).

The investigators have to explain the objectives of this trial and every surgical detail to the patients or their families, and the informed consent form must be signed before allocation. For those patients with surgical sequelae, this study provides ancillary and post-trial care according to standard medical practice. The investigators have access to the final results, which will be published in international peer-reviewed journals and shared in professional medical conferences. The raw data can be available from the corresponding author upon reasonable request. Patients' information will be de-identified and videos will be mosaicked before exhibition.

DISCUSSION

To the best of our knowledge, the PASTS-CD study is the first prospective RCT study directly comparing the efficacy and safety of GPi-DBS and STN-DBS for refractory CD patients. The results of this trial will be a powerful guide for neurosurgeons in the selection of DBS targets for CD patients.

One notable advantage of this trial is that the primary outcomes are quantified by standardized videos centrally and blindly by two neurologists. The customized scheme of standardized video recording has been tested to suffice for the scoring of the TWSTRS-severity subscale and Tsui scale. This design will eliminate the measurement bias from different scale raters of different centers and the interviewer bias from the subjectivity of scale raters. Another advantage is that this trial controls the confounding effect of electrode implantation accuracy, which is considered to be the most relevant factor to DBS efficacy.[42, 43] Due to the small size of the subcortical nuclei and the complex surrounding structures, a minor deviation from the target will bring about a significant disparity in DBS efficacy and adverse effects. Through measuring the distance between the sensorimotor subregion of target nuclei and the contacts of electrodes, the investigators exclude those subjects in which the volume of tissue activated (VTA) of DBS electrodes is speculated to show no or a low overlapping with the sensorimotor subregion of target nuclei. According to previous experiences[44, 45] and the volume difference between the two targets, the cutoff distance is defined to be 3mm for the STN-DBS group and 5mm for the GPi-DBS group. This procedure also minimizes the influence of technical discrepancy of different neurosurgeons. One possible limitation is that the neurosurgeons are not blinded, but this is determined by the nature of the surgical intervention. In fact, the main role of neurosurgeons is implanting the DBS electrodes into the predefined subregion of the two subcortical nuclei, and they do not participate in the subsequent scales scoring and DBS programming. As such, by controlling the accuracy of electrode position, the accompanying bias from the unblinded neurosurgeons will be significantly reduced. In addition, owing to the low incidence of CD, the investigators have to initiate a multicenter study to meet the requirement of sample size. Although multicenter studies may increase heterogeneity to some extent, it is believed that strict protocol implementation, coupled with systematic training and constant study monitoring, will help to minimize the biases and maximize the reliability of results.

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Contributors

Study conception: MZQ and YXG. Initial study design: LB and XJP. Revision of study design and protocol: MZQ. statistical analysis: YHN. Study coordination: YXG. Drafting the manuscript: LB and XJP. All authors read and approved the final manuscript.

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Figure legend

Figure 1 Flow chart of the PASTS-CD study. GPi, globus pallidus internus; STN, subthalamic nucleus; DBS, deep brain stimulation.

1

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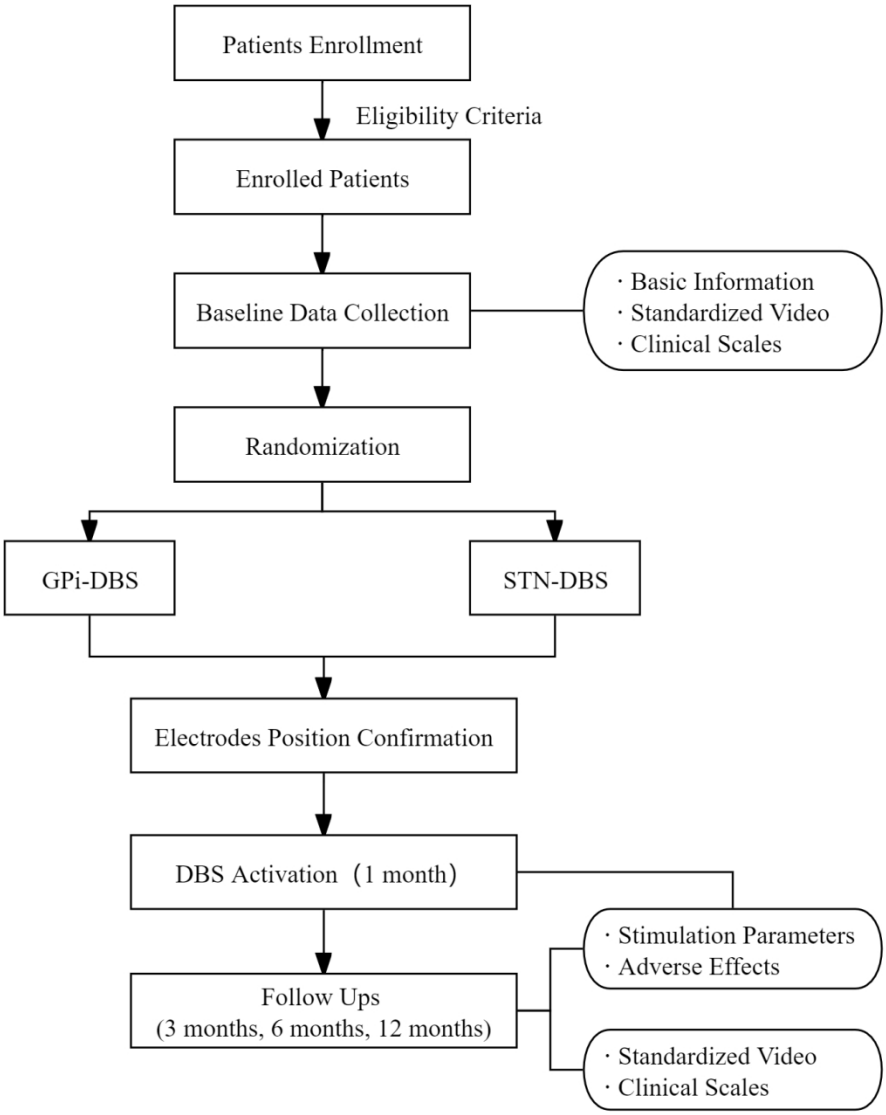

Figure 1 Flow chart of the PASTS-CD study. GPi, globus pallidus internus; STN, subthalamic nucleus; DBS, deep brain stimulation.

529x651mm (72 x 72 DPI)

Scheme of Standardized Video Recording

1. Seated position. (The patient wears a surgical cap with head, neck and shoulders on camera.)

① Eyes closed (20 seconds: 10 seconds recorded from the front and 10 seconds from the side).

Say to the patient, "Please sit down, close your eyes, and put your head where you feel most comfortable."

② Eyes open (10 seconds: 5 seconds recorded from the front and 5 seconds from the side).

Say to the patient, "Please sit down, open your eyes, and try to look straight ahead and keep your head in the middle."

③ Turn head right and turn head left (5 seconds each)

Say to the patient: "Look forward to the camera, turn your head to the right as far as you can, and then turn your head to the left as far as you can."

④ Head up and head down (5 seconds each)

Say to the patient: "Look forward to the camera, raise your head as high as you can, and then lower your head as low as you can."

⑤ Put the ear close to the right shoulder and then the left shoulder (5 seconds each).

Say to the patient, "Look forward to the camera. Now bring your right ear as close to your right shoulder as possible, and do not move your right shoulder."

Say to the patient, "Look forward to the camera. Now bring your left ear as close to your left shoulder as possible, and do not move your left shoulder."

⑥ Symptom persistence

Ask the patient, "If you divide your awake time during the day into four equal parts, how many parts do neck abnormalities take up?"

⑦ Symptom characteristics

Ask the patient, "Does each episode come on suddenly or gradually?"

⑧ Anterior view (Stop timing until the head is 10 degrees off center. Up to 60 seconds)

Say to the patient, "Please try to put your head in a straight position and look forward to the camera for one minute. Now start the clock."

⑨ Rest (10 seconds)

Say to the patient, "Rest for 10 seconds."

⑩ Anterior view (Stop timing until the head is 10 degrees off center. Up to 60 seconds)

Say to the patient, "Please do it again. Try to put your head in a straight position and look forward to the camera for one minute. Now start the clock."

⑪ Sensory tricks

Say to the patient, "Are there some movements or postures you can do to straighten your head? If so, try to do it."

2. Standing position (Show the whole body)

① Anterior view (5 seconds)

Say to the patient, "Please stand up and face the camera."

② Lateral view (5 seconds)

Say to the patient, "Please turn 90 degrees to the left (or right)."

3. Walking (10 seconds)

Say to the patient, "Please walk forward to the door and turn back."

Checklist

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title Page
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1, 8
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	Title Page
Funding	#4	Sources and types of financial, material, and other support	9
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	Title Page, 9
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a (no sponsor)
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a (no sponsor)
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	1-2

Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	1
Objectives	#7	Specific objectives or hypotheses	2-3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	3
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	3
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4-5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	4
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5-6

Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	3
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5-6, 6-7

Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a This trial sets two study mornitors (Page 7-8) instead of DMC.
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a No interim analyses (Page 7-8)
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	8

Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	8
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	9
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	8
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	8
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	8
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary materials
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a