Study protocol for Subthalamic Nucleus and Globus Pallidus Internus Deep Brain Stimulation in Patients With Primary Dystonia: a multicentre randomized controlled trial（RELAX Study）

NCT03017586

Date: 05/26/2017

Author: Lin Wang, Huifang Shang, Lingjing Jin, Yi Guo, Xinhua Wan

Affiliation and organization:

1. Department of Neurology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College

2. Neurotoxin research center of Key Laboratory of Spine and Spinal Cord Injury Repair and Regeneration of Ministry of Education, Neurological Department of Tongji Hospital, School of Medicine, Tongji University

3. Department of Neurology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology

4. Neurology Department, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University

5. Department of Neurosurgery, West China Hospital, Sichuan University

6. Department of Neurology, Qilu Hospital, Shandong University

7. Department of Geriatric Neurology, The Affiliated Brain Hospital of Nanjing Medical University

8. Clinical Research Institute, Institute of Advanced Clinical Medicine, Peking University

9. Department of Neurosurgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College

10. Department of Neurosurgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology

11. Department of Functional Neurosurgery, The Affiliated Brain Hospital of Nanjing Medical University

12. Department of neurosurgery, Qilu Hospital, Shandong University

13. Department of Neurology, Laboratory of Neurodegenerative Disorders, West China Hospital, Sichuan University

Corresponder: Yi Guo, Xinhua Wan

Abstract

Background: Dystonia is a relatively rare group of movement disorders that often prove difficult to treat effectively. Nowadays, deep brain stimulation (DBS) has become widespread and established treatment for patients with dystonia. The bilateral stimulation of either the globus pallidus internus (GPi) or the subthalamic nucleus (STN) is effective and safe in improving clinical symptoms and quality of life for patients with dystonia. RELAX study is a multicenter, prospective, randomized study designed to evaluate the clinical effectiveness and safety of DBS in patients with dystonia.

Methods/Design: Participants will be recruited in approximately 10 centers across China. All patients will undergo genetic testing. Eligible participants with dystonia will undergo DBS implantation according to the target randomization. Then, participants will be randomized to one of two groups: the experimental group (EG) with DBS on or the control group (CG) with DBS off. The primary outcome measures will focus on the changes in the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) movement scores, specifically assessed at three and six months of treatment. Secondary outcome measures, including specific item scores on the Short-Form General Health Survey (SF-36), Visual Analog Scale (VAS), walking measurements, the Beck Depression Inventory (BDI), Mini-Mental State Examination (MMSE), and the rate of improvement of the BFMDRS score, were all observed and recorded at 3 and 6 months during the treatment period. The aim of this trial is to investigate the efficacy and safety of DBS in patients with primary dystonia and gain insight regarding the therapeutic effects of different targets. Discussion: This is a large sample, randomized controlled trial to comprehensively evaluate the effectiveness and safety of DBS in patients with dystonia of different target.

Trial registration: NCT03017586, clinicaltrials.gov, registered on January 11, 2017, https://www.clinicaltrials.gov/ct2/show/NCT03017586

Keywords: Dystonia, Deep brain stimulation, Subthalamic nucleus, Globus pallidus internus

Background

Dystonia is the third most common movement disorder, characterized by sustained or intermittent involuntary muscle contractions causing twisting and repetitive movements or abnormal postures [1]. Primary dystonia is the most common form of dystonia, comprises a group of idiopathic, incurable movement disorders that vary with respect to age at onset, body distribution, and genetic association, to be 16.4 per 100,000 individuals [2]. Primary dystonia is a severe motor disease, causing physical and social incapacity in patients, devastating with significant morbidity and mortality [3]. Botulinum toxin is recommended as first-line treatment for dystonia, but its efficacy is variable and may wane over time. Besides, botulinum toxin is useful in focal dystonia but is difficult to use in generalized dystonia. The pharmacological treatment of dystonia is more challenging, bearing poor results [4]. The deep brain stimulation (DBS), available since the late 1980s, has become more widespread and now has established efficacy in a range of medically refractory movement disorders, such as Parkinson's disease (PD) and essential tremor (ET) [5]. DBS for treatment of dystonia was approved by the US Food and Drug Administration under a Humanitarian Device Exemption in 2003 [2]. DBS is now applied worldwide and the benefit-to-risk ratio of the therapy for dystonia is under scrutiny [6]. Typically, the globus pallidus internus (GPi) is the primary and the most studied target in dystonia. Recently, subthalamic nucleus (STN) stimulation has also shown a good response rate [4]. Studies have demonstrated that either the GPi or the STN is effective and safe in improving clinical symptoms and quality of life for patients with dystonia [7]. To our knowledge, however, only few studies has directly compared the clinical effects of GPi and STN stimulations in patients with dystonia, and best target for DBS in dystonia is still unknown [7]. Thus, randomized controlled trial (RCT) evidence is needed to confirm the efficacy and safety of DBS in dystonia patients, gain insight regarding the therapeutic effects of different targets (STN and GPi). To this end, we designed present multicenter, prospective, randomized and controlled study in patients with primary dystonia.

Aims

The purpose of this study is to evaluate the safety and effectiveness of deep brain stimulation (DBS) of the subthalamic nucleus (STN) and globus pallidus internus (GPi) for primary dystonia.

Design and Methods

Trial design

The RELAX study (ClinicalTrials.gov ID: NCT03017586) is a double blind, randomized, multicenter trial designed to evaluate the clinical effectiveness and safety of DBS using new device (G104, E202, L301/L302, PINS, Inc., Beijing, BJ, China) on patients with primary dystonia. Based on strict inclusion and exclusion criteria, patients with dystonia will undergo rigorous screening for the study. A total of five follow-up surveys have been arranged for the research. After recruitment, in the follow-up V2, participants will undertake the implantation of lead and IPG according to the target randomization. After the implantation, participants will be randomized (1:1) to one of two groups: the experimental group (EG) or the control group (CG). The IPG of participants in EG will be turned ON, the IPG of participants in CG will be turned OFF for 3 months. After 3 months of stimulation in the blinded conditions, unblinding, the IPG of participants will turn ON and receive follow-up assessments for another 3 months. The clinical measurements for the two groups include the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS), the Short-Form General Health Survey (SF-36), the Beck Depression Inventory (BDI) et all. All outcomes will be calculated by blinded statisticians appointed by clinical research institute of Peking University following the end

of the trial. The protocol design is based on the guidelines of the Consolidated Standards of Reporting Trials (CONSORT) and Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT), and the study results will also be reported according to these guidelines. Informed consent will be obtained from all participants in accordance with the policies of the board.

Study setting

The trial will be conducted at approximately 10 investigative centers domestically. Other hospitals will be invited to join the study according to interest, feasibility, and resources. No single center could exceed 30% of all enrolled patients. The clinical investigators from each center will be responsible for screening eligible participants. The protocol has been approved by the Clinical Trial Ethics Committee of Peking Union Medical College Hospital and registered on ClinicalTrials.gov protocol system (Clinical Trials Identifier: NCT03017586).

Patient population and recruitment

The study population comprises 70 patients suffering from primary dystonia. A patient must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for the study. A neurologist specialized in movement disorders will assess the patients' eligibility for study participation.

Inclusion and exclusion criteria

In detail, the key inclusion criteria are:

1. Refractory primary (systemic, segmental) dystonia diagnosed by a movement disorders neurologist
2. Severe functional impairment despite optimal medical management, including failed botulinum toxin therapy
3. Ability to follow up with post-operative study visits
4. Patients and their relatives have reasonable surgery expectations
5. Volunteer to participate in clinical trials, and signed consent form
6. Age 6-60 years

Exclusion criteria are:

1. Pregnancy or plan a pregnancy
2. Good treatment with Non-invasive therapy
3. Dopamine reactive dystonia， Genetic degeneration， Paroxysmal dystonia， Secondary dystonia， Psychogenic dystonia
4. Brain MRI showing extensive brain atrophy or small vessel ischemic disease
5. Cognitive impairment(MMSE<24)
6. Severe depression or other serious mental illness
7. History of traumatic brain injury, tumor, or severe cerebrovascular disease
8. Severe brain atrophy (diagnosed by CT or MRI)
9. Hyperthermia therapy in implant parts
10. Abnormal in blood inspection, blood clotting disorders, liver and kidney dysfunction, or other clinical judgment cannot tolerate surgery
11. High blood pressure, serious heart diseases, or respiratory diseases
12. Diabetes
13. Long-term treatment of immunosuppressive or hormones

14. Implant pacemakers, defibrillators, cochlear and other nerve stimulators
15. Other diseases need frequent MRI examinations
16. Participated in any other clinical trials within 3 months
17. Reluctant or unable to implant surgery
18. Reluctant or unable to cooperate with follow-up
19. Other exclusion Criteria by researchers

Recruitment of participants

Participants will be recruited by placing advertisements and posters in clinics and directly at the participating centers. The recruitment information mainly includes eligibility criteria and contact details. A well-trained investigator in each participating center will be responsible for screening all potentially eligible patients based on the eligibility criteria and obtaining the informed consent.

Randomization and blinding

There are two step of randomization allocation in this study. Firstly, eligible participants will be randomly assigned to one of two targets (STN or GPi) after completing the baseline measurements. The random numbers will be used to create the participant numbers and order lists, which will be placed in opaque sealed envelopes and sent to the research centers. After implantation of the device, participants will be randomly assigned to one of two groups (EG group or CG group). The participants randomized to the EG undergoing the DBS stimulation, participants in the CG will be OFF the DBS stimulation for 3 months follow-up. The assignment sequence (based on computer-generated random numbers) will be produced by The Peking University Clinical Research Institute. The research clerk will keep copies of the order lists and participant numbers.

Throughout the study, with the exception of the study programmer, all participants and study staff (including investigators, trainers, and statisticians) will be blinded to the treatment allocation. Independent raters who have no therapeutic relationships with the participants and who are blind to the treatment conditions will conduct outcome assessments. The independent raters will be clinical neurologists who have received additional training on the use of the outcome assessments, had the opportunity to listen to conducted assessments, and received direct feedback regarding their assessments from supervisors. Loss of blinding may occur due to the magnitude of the therapeutic effect or any other subjective perception.

Outcomes measures

Primary clinical outcomes

The primary outcome measures will focus on the changes in movement scores on the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS), which will be specifically assessed after three and six months of treatment.

Secondary clinical outcomes

Secondary outcome measures, including specific item scores on the Short-Form General Health Survey (SF-36), Visual Analog Scale (VAS), walking measurements, the Beck Depression Inventory (BDI), Mini-Mental State Examination (MMSE), and the rate of improvement of the BFMDRS score, were all observed and recorded at 3 and 6 months during the treatment period.

Safety outcomes

The occurrence rate of adverse events (AEs)/serious adverse events (SAEs) are documented at the scheduled and unscheduled clinical visits will be used to evaluate the safety of DBS. The

investigators are responsible for the management of participants' AEs and SAEs. During assessments, the investigator will question the participants about the occurrence of AEs and record the information in the source documents and patient case report form (CRF). The clinician will turn off the DBS therapy and evaluate the vital signs of the participant if the SAE occurs, then the suited therapy would be given for the participant. The investigators may choose hospitalization, outpatient treatment, home visits, communication, or other follow-up methods. All incidents are reported to the regulatory authority. All safety-relevant events are promptly reported tothe ethics committee and the safety monitor within 24 hours.

Sample size and power calculations

The study concerns the improvement of dystonia between EG and CG in terms of BFMDRS score in the 3 months follow-up. According to the results of study, which design is basically the same as this trial. With a power setting of 80% and calculations based on two-sided 95% confidence intervals, the study required 17 pairs for GPi and 14 pairs for STN. We assume that 10% of the trial participants will be lost to attrition. Thus, a total of 70 participants need to be allocated to each treatment group.

Statistical analysis

All evaluations of effectiveness and safety will be conducted according to the intention-to-treat (ITT) principle. The final data will be analyzed using IBM SPSS 13.0 or higher (SPSS, Inc., Chicago, IL, USA) and SAS 9.4 or higher (SAS Institute Inc., Cary, NC, USA) software. A p-value < 0.05 will be considered statistically significant. Data will be analyzed with t-tests and $\chi 2$ tests for continuous variables and categorical variables, respectively.

Quality assurance/monitoring

Monitoring is performed by the Data and Safety Monitoring Board (DSMB). DSMB will review the safety, ethics, and outcomes of the study. It is independent from the sponsor and has no competing interests.

Data management

Data collection will be restricted to the those meet the eligibility criteria. Participants who withdraw from the study for any reason will be recorded in their medical records and reviewed by the trial monitor.

Withdrawal and terminate from the study

In case of unexpected harm to the patient, insufficient compliance, or withdrawal of informed consent, a patient will promptly be excluded from further study treatment. The reasons for withdrawal must be documented in the CRF.

Handling of Missing Data

All variables included in the CRF are mandatory. The method last visit carried forward will be used to handle the missing data.

Data auditing

This trial will be audited by the Research Ethics Committee and the China Food and Drug Administration. The audits will be performed when the first participant enrollment, half and all of the enrolled cases are completed.

Discussion

Dystonia is a movement disorder characterized by abnormal movements or postures. There are many different clinical manifestations and underlying causes. This potentially debilitating disease can cause various problems, leading to impaired health-related quality of life [8]. Deep brain stimulation (DBS) is a well-established surgical treatment for patients with dystonia refractory to medical

treatment including botulinum toxin injections [8-10]. Although DBS is a well-established treatment for dystonia, there is significant heterogeneity in treatment effect and few data are available to identify ideal surgical candidates [11]. It is widely understood that the GPi and STN have been two used targets in DBS surgery with robustly reduce the BFMDRS score. However, the optimal choice is still debate [12-14]. Additionally, its reported that the different subtypes of dystonia also contribute to the variation of DBS outcome [15-16].

This multicenter double-blind randomized clinical trial will enable us to evaluate the effect and potential side effects of DBS stimulation in patients with dystonia. We hope to exploring the relative effectiveness of different targets (GPi vs STN) after follow-up periods. This study has several strengths. First, group-assignment in the double-blinded phase was randomized. Second, we performed a power calculation for this study. Most important of all, this outcome might influence the target selection and patients who are candidates for DBS to treat dystonia.

Trial status

The trial is ongoing and is actively enrolling. Target enrollment for this study is 70 participants.

Protocol version

The protocol version 1.1, PINS-DBS-1601, 05/26/2017.

Abbreviations

AEs, adverse events; BFMDRS, Burke-Fahn-Marsden Dystonia Rating Scale; BDI, Beck Depression Inventory; CONSORT, Consolidating Standards of Reporting Trials; CG, control group; CRF, case report form; DBS, deep brain stimulation; DSMB, Data and Safety Monitoring Board; EG, experimental group; ET, essential tremor; GPi, globus pallidus internus; ITT, intention-to-treat; MMSE, Mini Mental Status Examination; PD, Parkinson's disease; RCT, randomized controlled trial; STN, subthalamic nucleus; SF-36, Short-Form General Health Survey; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; SAEs, serious adverse events; VAS, Visual-analogue scale.

Acknowledgements

We would like to thank the entire team of researchers, including the nurses and staff at all 10 hospitals, for their determination, professional skills, enthusiasm, and effort.

Funding

This study was supported by Beijing biomedical industry leapfrog development project (G20), No. Z181100002218011.

Availability of data and material

Data from this randomized controlled study are unavailable at the time of publication. Individual participant data is available upon request.

Author contributions

Conception and design: Yi Guo, Lin Wang, Lingjing Jin; Study coordination: Huifang Shang, Xinhua Wan; Acquisition of legal authorization and data: Yi Guo and Xinhua Wan; Drafting and writing of the manuscript: Lin Wang, Huifang Shang, Lingjing Jin; Revision the approval of the final version of the manuscript:Yi Guo and Xinhua Wan; All authors reviewed and approved the final version of the manuscript.

Ethics, consent, and participants

The study will be conducted according to the Good Clinical Practice Guidelines and the principles of the Declaration of Helsinki. Written informed consent will be obtained from each participant.

The study protocol was approved by the Medical Ethics Committee Board of every center. To make any amendments to the protocol (Protocol Number: PINS-DBS-1601; Date: 05/26/2017), approval will be sought from the Institutional Review Board of Peking Union Medical College hospital. Informed consent must be provided in standard writing, the investigators elaborate the content to the participants. Informed consent will be provided by all participants, including their consent regarding the publication of the results to the investigators. Confidentiality will be ensured during all handling of the data. This study has been approved by Ethics Committee of Peking Union Medical College Hospital.

Consent for publication

Not applicable.

Competing interests

The authors declared that they have no competing interests

Reference

1. Vidailhet M, Vercueil L, Houeto JL, Krystkowiak P, Benabid AL, Cornu P, et al: Bilateral DeepBrain Stimulation of the Globus Pallidus in Primary Generalized Dystonia. N Engl J Med 2005, 352(5):459-467.

2. Dietz N, Neimat J: Neuromodulation Deep Brain Stimulation for Treatment of Dystonia. Neurosurg Clin N Am 2019, 30(2):161-168.

3. Borgohain R, Mridula RK, Tandra S: Deep brain stimulation in dystonia: The current status. Neurol India 2017, 65(6):1234-1235.

4. Cecchi F: Is deep brain stimulation (DBS) a safe and effective treatment for adults with dystonia? - A Cochrane Review summary with commentary. NeuroRehabilitation 2019, 18.

5. Harding KE, Robertson NP: Deep brain stimulation for dystonia. J Neurol 2016, 263(5):1045-1046.

6. Volkmann J, Wolters A, Kupsch A, Müller J, Kühn AA, Schneider GH, et al: Pallidal deep brain stimulation in patients with primary generalised or segmental dystonia: 5-year follow-up of a randomised trial. Lancet Neurol 2012, 11(12):1029-1038.

7. Lin S, Wu Y, Li H, Zhang C, Wang T, Pan Y, et al: Deep brain stimulation of the globus pallidus internus versus the subthalamic nucleus in isolated dystonia. J Neurosurg 2019, 8:11-12.

8. Tsuboi T, Wong JK, Okun MS, Ramirez-Zamora A: Quality of life outcomes after deep brain stimulation in dystonia: A systematic review. Parkinsonism Relat Disord 2019, 18. pii: S1353-8020(19):30492-30494.

9. Vidailhet M, Vercueil L, Houeto JL, Krystkowiak P, Lagrange C, Yelnik J, et al: Bilateral, pallidal, deep-brain stimulation in primary generalised dystonia: a prospective 3 year followup study. Lancet Neurol 2007, 6(3):223–229.

10. Kupsch A, Benecke R, Müller J, Trottenberg T, Schneider GH, Poewe W, et al: Pallidal deep-brain stimulation in primary generalized or segmental dystonia. N Engl J Med 2006, 355(19):1978-90.

11. Badhiwala JH, Karmur B, Elkaim LM, Alotaibi NM, Morgan BR, Lipsman N, et al: Clinical phenotypes associated with outcomes following deep brain stimulation for childhood dystonia. J Neurosurg Pediatr 2019, 12:1-9.

12. Wu YS, Ni LH, Fan RM, Yao MY: Meta-Regression Analysis of the Long-Term Effects of Pallidal and Subthalamic Deep Brain Stimulation for the Treatment of Isolated Dystonia. World Neurosurg 2019, 129:e409-e416.

13. Meoni S, Fraix V, Castrioto A, Benabid AL, Seigneuret E, Vercueil L, et al: Pallidal deep brain stimulation for dystonia: a long term study. J Neurol Neurosurg Psychiatry 2017, 88(11):960- 967.

14. Deng Z, Pan Y, Zhang C, Zhang J, Qiu X, Zhan S, et al: Subthalamic deep brain stimulation in patients with primary dystonia: a ten-year follow-up study. Parkinsonism Relat Disord. 2018, 55:103-110.

15. Alterman RL, Filippidis AS: Genetic Subtypes and Deep Brain Stimulation in Dystonia. Mov Disord Clin Pract 2018, 5(4):357-360.

16. Jinnah HA, Alterman R, Klein C, Krauss JK, Moro E, Vidailhet M, et al: Deep Brain Stimulation for Dystonia: A Novel Perspective on the Value of Genetic Testing. J Neural Transm (Vienna) 2017, 124(4):417-430.