

BMJ Open Early versus Late Application of Subthalamic deep brain Stimulation to Parkinson's disease patients with motor complications (ELASS): protocol of a multicentre, prospective and observational study

Lulu Jiang,¹ Wai Sang Poon,² Elena Moro,³ Wenbiao Xian,¹ Chao Yang,⁴ Xian Lun Zhu,² Jing Gu,⁵ Xiaodong Cai,⁶ Jinlong Liu,⁴ Vincent Mok,⁷ Yanmei Liu,¹ Shaohua Xu,¹ Qiyu Guo,¹ Wanru Chen,¹ Ling Chen¹

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ABSTRACT

Introduction Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a well-established surgical treatment for Parkinson's disease (PD). However, there is currently no consensus on the best timing for this surgery. The aim of our study is to compare the therapeutic efficacy of bilateral STN DBS in patients with PD with early and late motor complications.

Methods and analysis 200 patients with PD will be enrolled in this multicentre, prospective, observational study, and will be followed up for 4 years. Patients with PD who meet the criteria for STN DBS surgery will be allocated to either the early stimulation group or the late stimulation group based on the duration of their motor complications. The primary outcome will be changes in quality of life from baseline to 4 years, measured using the 39-item Parkinson's Disease Questionnaire Summary Index. The secondary outcomes include changes in motor function measured using Movement Disorder Society-revised Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III, self-reported experiences of daily living measured using MDS-UPDRS Part I B and Part II, good 'on' time recorded by the patients using a diary and safety profile of both groups.

Ethics and dissemination The study received ethical approval from the Medical Ethical Committee of the First Affiliated Hospital, Sun Yat-sen University. The results of this study will be published in peer-reviewed journals and presented at international conferences.

Trial registration number NCT01922388; Pre-results.

INTRODUCTION

Background and rationale

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. Based on worldwide data, the prevalence of PD is 428/100 000 in people aged between 60 and 69 years,

Strengths and limitations of this study

- The study is a multicentre research study with sufficient sample size and long-term follow-up duration.
- The study will provide evidence for neurologists in strategy selection when treating patients with Parkinson's disease (PD).
- The study is observational.
- There is a risk of recruiting patients with non-idiopathic PD despite our strict inclusion criteria.

1087/100 000 in people aged between 70 and 79 years and 1903/100 000 in people over the age of 80 years.¹ Nowadays medical treatment still remains most effective for the management of PD, but patients will eventually develop motor complications after prolonged use of medications, including motor fluctuation and dyskinesia. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has been demonstrated to improve motor symptoms and complications better than the most effective oral medications approved for advanced PD.²⁻⁴ However, there is currently no consensus on the optimal timing for performing DBS during the course of the disease. Recommendations from experts in this field support the use of DBS only when medications fail to adequately control symptoms or cause severe side effects because of the potentially serious risks that are associated with surgery and neurostimulation.⁵ However, more recently, DBS has been considered earlier for therapeutic intervention with the aim of improving the quality of life in patients during the course of the disease.⁶



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For numbered affiliations see end of article.

Correspondence to

Dr Ling Chen;
chenl2@mail.sysu.edu.cn

In 2007, a French pilot study showed that STN DBS was more effective than oral medications for early stages of PD (disease duration of 6.8 ± 1.0 years).⁷ In 2013, results from a large-scale trial (the EARLYSTIM study) showed superiority of STN DBS for treating patients with PD with early motor complications compared with the best oral medications available. This was evaluated based on quality of life, motor function and motor complications during a 2-year follow-up study.⁸ A recent retrospective study reported that early-stimulated patients might have better long-term outcome in the activities of daily living during 'OFF-condition' (assessed by Unified Parkinson's Disease Rating Scale (UPDRS) Part II) than with late-stimulated patients.⁹ Given these findings, it might be better for patients with PD to have DBS surgery earlier. While there may be risks that non-idiopathic patients with PD might be included, the benefit-to-risk ratio could possibly be lower for patients undergoing STN DBS just after the onset of motor complications.¹⁰ To our knowledge, there is currently no ongoing study examining the differences in long-term efficacy and safety between early STN DBS-stimulated and late STN DBS-stimulated patients with PD.

Objectives

Early versus Late Application of Subthalamic deep brain Stimulation (ELASS) study was initiated in 2013, and is anticipated to be concluded by 2020. The primary objective of this study is to demonstrate statistically significant difference in quality of life (39-item Parkinson's Disease Questionnaire Summary Index (PDQ-39 SI)) and improvement in patients with PD with early and late motor complications measured from baseline to 4 years after DBS surgery. Additional objectives are to summarise or characterise the following: changes in motor function (Movement Disorder Society (MDS)-UPDRS III) from baseline (off medication) to 4 years (off medication/on stimulation); changes in self-reported experiences of daily living (MDS-UPDRS Part I B and Part II) from baseline to 4 years; changes in good 'on' time (using a patient diary) from baseline to 4 years; changes in cognition, emotion and non-motor symptoms from baseline to 4 years and safety profiles for both groups based on severe adverse effects reported throughout the study.

METHODS AND ANALYSIS

Study design and setting

ELASS is a Chinese, multicentre, prospective and observational study. Patients will be recruited by three centres in China, comprising (1) the First Affiliated Hospital of Sun Yat-Sen University (affiliation of the principal investigator; PI), Guangzhou; (2) the Prince of Wales Hospital, Hong Kong and (3) the Shenzhen Second People's Hospital, Shenzhen. Patients will be allocated to groups based on the duration of their motor complications at the time of recruitment. Those with motor complications of 3 years or less will be assigned to the early stimulation

group⁸ and the remaining patients allocated to the late-stimulation group.

Eligibility criteria

Inclusion criteria

Patients will be eligible for recruitment if they meet the following criteria: (1) a diagnosis of idiopathic PD based on the British brain bank criteria; (2) disease duration ≥ 4 years; (3) good response to levodopa, that is, more than 30% improvement¹¹⁻¹³ in motor function after an acute levodopa challenge test, assessed using the MDS-UPDRS¹⁴ Part III; (4) presence of motor fluctuation and/or dyskinesia; (5) age range between 18 and 75 years old; (6) normal brain MRI; (7) absence of dementia (Mini-Mental State Examination (MMSE) ≥ 26); (8) absence of severe psychiatric diseases; (9) completed informed consent forms.

Exclusion criteria

Patients with one of the following conditions will be excluded: (1) presence of severe metabolic diseases, (2) severe cardiac/respiratory/renal/hepatic diseases, (3) secondary parkinsonism or multiple system atrophy, (4) illiteracy or insufficient language skills to complete the questionnaires, (5) poor compliance or unrealistic expectations, (6) women who are pregnant or breast feeding, (7) simultaneous participation in another clinical trial.

Procedures

Baseline assessment

Patients with PD with an intention of receiving DBS will be screened and recruited by neurologists in an outpatient clinic. When a patient decides to participate in the study, the informed consent form (ICF) will be signed and personally dated by the patient or legally authorised representative and the investigator. One copy of the signed ICF will be sent to the PI's institute and one will be kept in the patient's binder at the investigation site. After the recruitment, there will be at least a month for observation and preparation. During this period, drug regimens will remain unchanged and patients will have to complete the PD home diary¹⁵ for three consecutive days for a period of two consecutive weeks. They will then be admitted to the neurology department for preoperative evaluation, which includes (1) motor function in both 'off' and 'on' states, accessed using MDS-UPDRS Part III; (2) dyskinesia, accessed using Unified Dyskinesia Rating Scale;¹⁶ (3) quality of life, accessed using the PDQ-39;¹⁷ (4) sleep, accessed using the Parkinson's Disease Sleep Scale-Chinese Version¹⁸ and the Pittsburgh Sleep Quality Index;¹⁹ (5) emotion, accessed using the Hamilton Anxiety Scale, the Hamilton Depression Scale²⁰ and the Beck Depression Inventory;²¹ (6) cognition, accessed using the MMSE²² and the Montreal Cognitive Assessment;²³ (7) non-motor symptoms, accessed using the Non-Motor Symptoms Scale;²⁴ (8) brain MRI. Those who meet the inclusion criteria will be transferred to the

neurosurgery department for implantation of the DBS device. Patients who fail the inclusion criteria will be excluded from the study. Follow-ups will be scheduled for 1 year and 4 years after surgery.

Motor symptoms will be assessed using two conditions (off medication and on medication) preoperatively, and in four conditions (off medication/on stimulation, off medication/off stimulation, on medication/off stimulation and on medication/on stimulation, consecutively) postoperatively. The off medication state is defined as the motor function after withdrawal of anti-parkinsonian medications for at least 12 hours. The on medication state refers to the condition when medications take their full effect. One hundred and fifty per cent of the normal morning dose will be used for the preoperative levodopa challenge test and the same dose will be used for each follow-up. Medications will be converted into an equivalent dose of immediate-released levodopa (Madopar) for administration, based on the following formula²⁵: 100 mg immediate-released levodopa=133 mg controlled-released levodopa=1 mg pramipexole=100 mg piribedil=10 mg selegiline; each dose of levodopa is 25% more effective with entacapone. The off/on stimulation state will be assessed at least half an hour after switching off/on the device.

Surgery

All centres have the expertise to perform DBS surgery, with surgeons having more than 5 years of experience at the start of the trial. Surgical procedures between each centre may differ, but the following requirements will be met to guarantee an optimal approach: (1) targeting and trajectory planning will be based on the fusion of non-stereotactic MRI scans with stereotactic CT scans. (2) Electrode implantation can be done under either local or general anaesthesia, but microelectrode recordings (MER) will be mandatory for all patients. During the MER in the STN, passive movement of the contralateral limbs will be performed to observe whether there are any movement-related neuronal firing changes. In cases where general anaesthesia is used, somatosensory evoked potentials elicited by median nerve stimulation will be used to facilitate localisation of the STN.²⁶ Test stimulations will be applied to patients under local anaesthesia to monitor improvements of parkinsonian signs and stimulation-induced side effects. (3) Leads will be secured at the burr hole site using the Stimloc system (Medtronic, Minneapolis, Minnesota, USA). (4) The implantable pulse generator (IPG), either a rechargeable one (Activa RC, Medtronic) or a non-rechargeable one (Activa PC, Medtronic) will be implanted subcutaneously usually at the right subclavicular area, with in the same procedure for the electrodes.

Stimulation parameter programming

A month after surgery, patients will visit the clinic in the 'off' state for initial programming of electrical parameters for stimulation. The IPG will be turned on and all the

contacts tested based on a standard protocol. With the IPG as anode, the tested contact as cathode, pulse width of 60 μ s and frequency of 130 Hz, the amplitude will be gradually increased to 5–6 V in increments of 0.5–1 V or until side effects are intolerable. Tremor and rigidity of the tested limbs will be scored and all adverse effects, if any, will be recorded each time the amplitude is increased. The electrode contacts with the lowest threshold for inducing a benefit and the highest threshold for side effects will be selected for chronic stimulation. Initial stimulation parameters will be set at 60 μ s and 130 Hz, with variable voltages (usually 1.0–2.0 V). If results are not satisfactory by voltage adjustments only, further modification to parameters will include pulse width, frequencies or configurations. Subsequent programming sections to the parameters and medications will be progressively adjusted to achieve maximum improvement.

Sample size

Given that it is easier to recruit patients with motor complications of more than 3 years, we decide that n_B , the size of the late stimulation group, should be twice n_A , the size of the early stimulation group. Calculation of the sample size will be based on the primary outcome of quality of life measured using PDQ-39 SI. Based on retrospective analysis of our previous data, the adjusted mean improvement of PDQ-39 SI from baseline to 3 years after DBS surgery was 16.7 ± 11.43 in 15 patients with early motor complications, and 11.2 ± 12.05 in 29 patients with late motor complications. A two-sample test will be used to determine if the mean of the early group (μ_A) is different from that of the late group (μ_B). The hypotheses is: $H_0: \mu_A - \mu_B = 0$, $H_1: \mu_A - \mu_B \neq 0$. The sample size will be calculated using the PASS V.11 sample size calculation software. Based on tests for two means, with a two-sided significance level of 5% and statistical power at 80% and allowing for a 20% dropout rate, a sample size of 200 patients will be needed to test the hypothesis with the two-sided test. This will consist of 67 patients for the early group and 133 for the late group.

Outcome measurements

Primary outcome: changes in quality of life measured using PDQ-39 SI from baseline to endpoint.

Secondary outcomes will be measured based on:

1. Changes in motor function measured using MDS-UPDRS Part III scores from baseline to endpoint;
2. Changes in good 'on' time, including 'on' without dyskinesia and 'on' with non-troublesome dyskinesia based on PD home diary, from baseline to endpoint;
3. Changes in MDS-UPDRS patient questionnaire (Part I B and Part II) scores from baseline to endpoint;
4. Safety profile of both groups based on severe adverse effects reported through the 4-year study duration.

Data collection methods

Assessment of safety

Safety data will be inclusive of all adverse effects (AEs), from the point of subject enrolment to the final follow-up

visit or discontinuation, whichever comes first. Reports of AEs will minimally include the following information; date of event; diagnosis or description of the event; assessment of the seriousness; treatment; outcome and date.

Collection of data

Before the start of the study, investigators from each centre will be trained on proper data recording. Data collected from each patient will be transcribed in a paper case report form (CRF) and sent to the PI's centre every half a year. A copy of the CRF will be placed in the subject's binder at the investigation site. Three monitors will audit the contents of the CRF before being entered into the database. Personal data will be coded and made anonymous.

Statistical methods

The parameters of interest will be mean changes of the observed values from baseline to 4year follow-up. Our hypothesis is that the average change of PDQ-39 SI in the early group (μ_A) will be statistically different from that of the late group (μ_B): $H_0: \mu_A - \mu_B = 0$, $H_1: \mu_A - \mu_B \neq 0$. The primary analysis will be a complete case analysis (ie, using only cases with complete data), supported by sensitivity analysis, where missing data will be filled in using the multiple imputation method. The number, timing, pattern and reason for missing data or dropout will be reported, as well as their possible implications in efficacy and safety assessments. Statistical analysis of the primary and secondary endpoints will be performed within the framework of the generalised linear model with baseline adjustment. Covariates including age, disease duration, baseline motor scores and baseline PDQ-39 SI scores will be introduced into the linear model. Main effects (group and time), effects of covariates, group-by-time interaction and group-by-covariate interaction will be calculated and analysed using analysis of covariance. Summaries of continuous variables will be presented as means (\pm SD) for normally distributed data and as medians with interquartile ranges for skewed data; categorical variables will be presented as frequencies (percentages). Statistical analysis will be performed using the SPSS V.13.0. All statistical tests will be two-tailed, and a P value of less than 0.05 is considered to indicate statistical significance.

ETHICS AND DISSEMINATION

Any amendments to the study will be submitted to the local ethics committee for review. Signed informed consent forms will be required for each patient enrolled. Final study results and conclusions will be presented at international conferences and publications in peer-reviewed journals.

Author affiliations

¹Department of Neurology, National Key Clinical Department and Key Discipline of Neurology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, China

²Department of Surgery, Division of Neurosurgery, Prince of Wales Hospital, Chinese University of Hong Kong, Shatin, Hong Kong, China

³Division of Neurology, Centre Hospitalier Universitaire de Grenoble, Grenoble, France

⁴Department of Neurosurgery, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

⁵Department of Medical Statistics and Epidemiology, School of Public Health, Sun Yat-sen University, Guangzhou, China

⁶Department of Neurosurgery, Shenzhen Second People's Hospital, Shenzhen University, Shenzhen, China

⁷Department of Medicine and Therapeutics, Division of Neurology, Prince of Wales Hospital, Chinese University of Hong Kong, Shatin, Hong Kong, China

Contributors LC, WSP, EM and XLZ contributed the conception and design of the study. CY, WX, JG, XC, JL and VM provided their area of expertise for protocol development. YL and SX arranged the meetings and took the minutes. QG and WC were responsible for the statistics. LJ drafted the manuscript. All authors revised the manuscript and provided feedback and comments. LC approved the final version of the manuscript prior to submission. LJ took responsibility for the submission process.

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Competing interests None declared.

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