Interleaving stimulation improving dyskinesia in Parkinson's disease: randomized, double-blind, controlled trial

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Version 1.5

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Study protocol

1. Background

The clinical utility of deep brain stimulation (DBS) for the treatment of Parkinson's disease (PD) has been well established; however, there are a variety of adverse events, such as dyskinesia among subthalamic nucleus (STN) DBS recipients due to varied postoperative management. The artificial electrical signals of deep brain stimulation are delivered with four parameters; contact (0~3), frequency (Hertz - Hz), amplitude (voltage or current) and pulse width (microseconds, μs). It has recently been reported that interleaving stimulation can be used effectively to treat motor symptoms while avoiding side effects.

Dyskinesia

Levodopa-induced dyskinesias (LIDs) are motor complications of Parkinson's disease. LID is characterized by progressive motor disability and may interfere with quality of life.

STN-DBS has also been demonstrated to provoke or exacerbate dyskinesia (stimulation-induced dyskinesia, SID). Previous studies have showed that the proportion of stimulation-induced dyskinesia is as high as 50% to 75%.

Both kinds of dyskinesias have variable phenotypes, including chorea, ballism, dystonia, myoclonus, or combination of any of these movements. SIDs are easily evoked in patients with severe preoperative LIDs.

In general, reducing the dosage of levodopa can improve LIDs post-operation. However, this approach will fail when dyskinesia is the result of stimulation. Available programming, such as interleaving stimulation could improve dyskinesias post-operation.

So, this study is designed as a prospective, **randomized, double-blind, controlled** study to assess putative differences in the effect of interleaving stimulation and empirical stimulation with regards to post-operation dyskinesia control.

2. Study design

2.1 Purpose

The primary objective is to assess putative differences in the effect of interleaving stimulation and empirical stimulation with regards to dyskinesia control.

2.2 Primary Outcome Measures

The changes of dyskinesia scores (UPDRS IV, item 32 + item 33) in interleaving stimulation compared to empirical programming modes. *[Time Frame: 3 months and 9*

months]

The changes of Parkinson's disease quality of life-39 (PDQ-39) scores in interleaving stimulation compared to empirical programming modes. *[Time Frame: 3 months and 9 months]*

2.3 **Secondary Outcome Measures**

The changes of scores of United Parkinson's Disease Rating Scale Part III in interleaving stimulation compared to empirical programming modes. *[Time Frame: 3 months and 9 months]*

Scores of neuropsychological Battery in interleaving stimulation compared to empirical programming modes. *[Time Frame: 3 months and 9 months]*

2.4 Safety outcome Measures

Adverse events *[Time Frame: up to 12 months]*

Any adverse medical event from date of randomization until the date of first documented adverse event or date of death from any cause, which ever comes first, assessed up to 12 months.

Persistent dyskinesia despite optimization of parameters of stimulation is defined with severity ≥2 on item 32 and duration ≥2 (e.g., duration ≥ up to 50% of the 16 hours ambulatory time) on item 33 of the unified Parkinson's disease rating scale (UPDRS) part IV.

2.5 Study population:

Indications of DBS for PD consistent with the China specific approved labeling.

Inclusion Criteria

- Patients at the age of 30–65 years old.
- Patients diagnosed as Parkinson's disease according to the UK Parkinson's Disease Society Brain Bank criteria.
- Patients at Hoehn and Yahr stage 3 or lower in the on-state and stage 2 - 4 in the off-state.
- The disease duration of 5 years or more.
- Patients with deep levodopa-responsive Parkinson's disease, and are not adequately controlled by drug therapy.

Study participants will be PD patients undergoing DBS of the subthalamic nucleus (STN). Whether or not a patient is selected for DBS surgery is determined by the patient's clinical team purely on independent clinical grounds. Only those patients who have been accepted for DBS treatment by their clinical neurologist and functional neurosurgeon will

be introduced to the project and have their details passed on to the research team for further information and formal inform consenting.

Exclusion Criteria

Exclusion criteria are: major illness or medical comorbidities, depression that is untreated but judged to be clinically significant by an investigator, cochlear implants, cardiac pacemakers, needs for diathermy, anticoagulant therapy, previous neuro-surgical procedure or ablative therapy, frank dementia according to cognitive screening, drug or alcohol abuse, being a woman of child-bearing potential, having a positive pregnancy test, or presence of a terminal illness.

Written informed consent is obtained from all patients before any study procedures were started.

3. Study Process

3.1 Randomization and masking

50 Patients will be randomly assigned to either the interleaving stimulation modes group (ISG) or the empirical stimulation modes group (ESG).

ISG: empirical stimulation for the first 3 months, followed by interleaving programming period for 6 months, and any stimulation decided by the neurologists/neurosurgeons for the final 3 months.

ESG: empirical programming for the first 9 months' period, followed by any stimulation decided by the neurologists/neurosurgeons for the final 3 months.

Patients are randomly assigned to receive either interleaving stimulation (interleaving group, 25 patients) or empirical stimulation (conventional group, 25 patients) after the enrollment, just before the implantation of the DBS device in the STN. The randomization ratio was 1:1 (Fig 1).

Randomization is done by computer-generated pairwise according to order of enrolment, so that similar numbers of patients are recruited to each study group. The chief investigator generates the randomization sequence. The randomization scheme is kept in sealed envelopes. The randomization sequence was revealed only to the unmasked clinician responsible for the stimulation programming, but not to the rater. Patients were masked to randomisation group.

3.2 Procedures

DBS devices (Medtronic, Neuromodulation, Minneapolis, USA) approved in China (Activa® RC 37086, Pocket Adapter: Model 64001 and 64002, Extension wire: 7482, DBS lead: 3387 or 3389) are implanted by use of MRI or CT fusion for targeting and microelectrode recording for target refinement, followed by intraoperative test stimulation of the DBS lead. The pulse generators were placed in a subclavicular position on the same day.

It is allowed to use existing DBS surgery equipment and is asked to physiologically refine the DBS targets based on the best medical practices. Devices implanted into patients are initially programmed (switched on) 28±5 days after surgical implantation (Week 0/ Month 0).

The patients will undergo bilateral STN DBS. Management of medication is the responsibility of the investigators at each site and was not protocol driven.

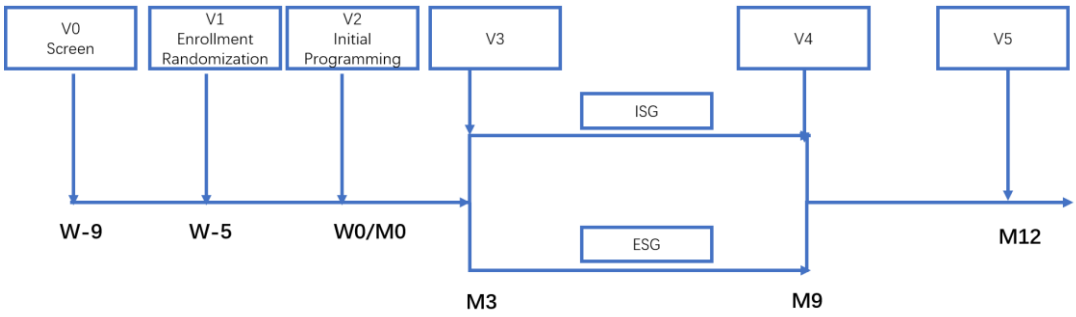
Over a 3-month period, each patient's parameters of stimulation and medications for Parkinson's disease are adjusted, based on clinical need and empirical stimulation to obtain the best clinical effect, no interleaving stimulation are allowed in this period.

At Month 3, patients are settled into either condition: with the empirical stimulation parameters or with the interleaving programming.

No routine programming plan is set during month 3 to month 9， unless the patient requires adjustment of stimulation parameters due to symptoms of Parkinson's disease or adverse effects of stimulation. The stimulation mode remains unchanged during this period and records the reason and parameters of each programming.

After month 9, the programmer can adjust the stimulation mode and parameters based on clinical need. The dopaminergic therapies are maintained stable since baseline and last in the entire duration of the study.

Fig 1



3.3 Surgical procedure

All patients have stereotactic guidance for the insertion of electrodes under local anesthesia. Leksell Frame-based stereotaxy is performed in most of the patients. The image targeting and trajectory are planned based on preoperative MRI. On the day of operation, a computed tomography (CT) scan of brain with the stereotactic frame fixed to the head is performed and fused to the MRI plan in the computer planning system. Microelectrode recording (MER) is introduced to obtain neuronal discharges for neurophysiological targeting. Macrostimulation is performed in all patients for target confirmation. Deep brain stimulation electrode is implanted if satisfactory signals from MER

and response from macrostimulation are obtained. The Pulse Generator is implanted under general anesthesia after CT scan made sure the target. The DBS is usually switched on at 4 weeks(28±5 days) after the operation. Movement disorder specialists take up DBS programming. In brief, Patients are settled with simple polar stimulation with combined parameters adjustment (monopolar mode, 60~90μs pulse width, 130~185Hz frequency and varied voltage) during the follow-up.

3.4 Programming Procedures

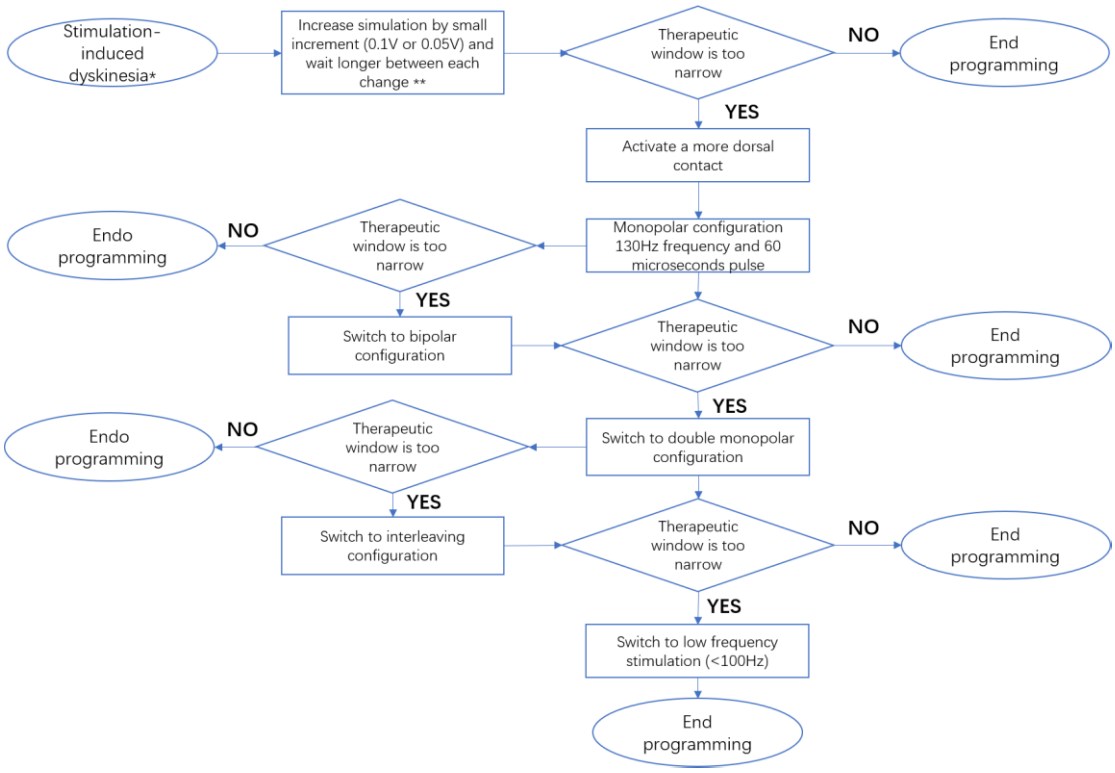
The settlement of stimulation parameters is best carried out by trained neurologists and depends to a large extent on personal experience. The detailed algorithms for a disease-specific programming strategy includes contact configuration adjustment and stimulation parameters selection. In general, each of the ring electrodes should be tested in a monopolar configuration with monopolar stimulation, 130 Hz frequency and 60 microseconds pulse width. Amplitude is slowly increased until satisfactory clinical benefit or manifestation of side effects. The selected contact is determined by the best clinical outcomes and largest therapeutic window. In order to achieve the best clinical effect, frequency and pulse width should be changed by motor symptoms. Stimulation frequencies of 50 Hz and 185 Hz improve all motor signs. Pulse width between 60 and 210 μs is beneficial for improving tremor and rigidity.

All patients receive conventional programming strategies to relieve their symptoms, but some achieve suboptimal results over time. Both levodopa inducing dyskinesia and stimulation inducing dyskinesia can happen after STN DBS. A useful strategy is decreasing the stimulation or dopaminergic medication, but some patients might experience a worsening in parkinsonism as a consequence. Unsatisfactory improvement of PD symptoms and dyskinesia, including choreoathetoid and dystonic movements, can be troublesome to patients. If patients do not improve adequately or if there are intolerable adverse effects (such as dyskinesia), interleaving stimulation (ILS) is tested to improve the symptom.

ILS consists of two rapid and alternate stimulation programs with different contacts, amplitudes, and pulse width but the same frequency up to a maximum of 125Hz. Contact selection is determined by postoperative stereotactic computed tomography and clinical evaluation to achieve a balance between motor improvement and tolerable side effects. For example, ILS is successfully applied for PD motor symptoms (stimulation of subthalamic nucleus) as well as dyskinesia (additional stimulation of zona incerta).

ILS may be applied either to limit dyskinesia or else, to stimulate different brain regions with individualized settings in order to alleviate specific symptoms. In accord with previous reports, dyskinesia is improved with additional more dorsal contact in a monopolar or bipolar fashion. Stimulation adjustment with lower amplitudes in the more dorsal contact (targeting the lenticular fasciculus) and higher amplitudes in a ventral contact (targeting the STN) might be able to control dyskinesias and parkinsonism.

Based on the standard algorithms and reconstruction images, we would choose and adjust the most suitable contacts and settings for ILS for each patient to improve their PD symptoms and alleviate dyskinesia. In addition, after ILS with one contact program, which gradually increases the amplitude and pulse width as necessary, ILS with another program selecting other specific contacts and settings, according to standard algorithms, with increased amplitude and pulse width can be performed to achieve further motor benefit and avoid adverse effects.



*: reduce medications at the same time to avoid peak-dose levodopa-induced dyskinesia and/or the worsening of stimulation-induced dyskinesia; **: training the patient on to use remote control may be a valid strategy;

4. Study assessment

4.1 Efficacy assessments

The primary efficacy endpoints are the changes of dyskinesia scores and the changes of PDQ-39 scores in interleaving stimulation compared to empirical programming modes. *[Time Frame: 3 months and 9 months]*

The secondary endpoints include the changes of UPDRS III scores and the changes of neuropsychological Battery scores in interleaving stimulation compared to empirical programming modes. *[Time Frame: 3 months and 9 months]*

The parameters in primary and secondary endpoints are also tested at baseline (Enrollment). After DBS activation (Month 0), patients are again assessed at Month 3, Month 9 and Month 12 in off-medication/on-stimulation and on-medication/on-stimulation, as shown in table 1. We defined “on-medication” as roughly 60 min after a patient takes

antiparkinsonian medication when both the clinician and the patient indicate that the medication dose is effective.

4.2. Clinical Assessment

This assessment includes clinical assessment, levodopa challenge test, video recording, neuroimaging, and neurocognitive aionnd psychiatric evaluations. The clinical evaluation is performed in the morning, after a 12-hour withdrawal of antiparkinsonian drugs. Assessment data are obtained before and after the operation (medication-off/ -on state and stimulationor-on) and include the MDS-UPDRS, Unified dyskinesia rating scale (UDysRS), modified Hoehn & Yahr stage (off/on-state), levodopa equivalent dose, and body weight. Motor assessments are videotaped, and two raters collected independent ratings.

Subjects are instructed to report any adverse event during the course of the study, including pulling (contractions), tingling, blurry vision, double vision, speech changes, or walking problems.

Table 1

Visit	V0 Screen	V1 Enrollment (Randomization and Surgery)	V2 Initial Programming	V3	V4	V5
Time (±5 days)	Week -9 ~Week -5	Week -5	Week 0 /Month 0	Month 3	Month 9	Month 12
Informed consent	X					
Inclusion criteria	X	X				
Exclusion criteria	X	X				
Randomization		X				
Medication	X	X	X	X	X	X
Programming			X	X	X	X
Pre-surgical assessments		X				
UPDRS III, IV		X	X	X	X	X
UDysRS		X	X	X	X	X
PDQ-39		X	X	X	X	X

Cognitive Tests		X			X	X
Adverse Events	X	X	X	X	X	X

5. Sample size and Statistical analysis

5.1 Sample size

According to the sample size estimation method of comparing the mean of two independent samples, 42 subjects are planned to be enrolled in this study. Increase the number of cases according to the 20% dropout rate, and finally enrolled 50 cases. In this study, the change scores of total scores of visit 5 (month 12) UPDRS IV comparation with baseline is the endpoint to use to calculate the sample size. The specific calculation method was as follows:

Use Power Analysis & Sample Size software 11 (SPSS 11) to calculate the sample size. The formula is as follows.

$$n = Ceiling\left\{\frac{(Z_{1-\alpha} + Z_{1-\beta})^2 \sigma_d^2}{2\delta_1^2}\right\}.$$

The non-inferiority hypothesis

Primary Outcome Measures

The changes of dyskinesia scores (UPDRS IV, item 32 + item 33)

H0: interleaving stimulation - empirical stimulation < 0.5 score

H1: interleaving stimulation - empirical stimulation ≥ 0.5 score

Significance level: α = 0.025 (unilateral),
Power: 1-β = 0.8,
Standard deviation of single group: SD = 1.1,

H0 is the null hypothesis, H1 is the alternative hypothesis. After subjects receiving interleaving stimulation, if the mean change scores of UPDRS IV equals or exceeds 0.5 points than that of those patients receiving empirical stimulation, then H0 will be rejected, non-inferiority conclusion can be made when comparing interleaving stimulation group with empirical stimulation group. If H0 can't be reject, the conclusion that the interleaving stimulation group is better than or equivalent to empirical stimulation group can’t be reached.

5.2 Statistical analysis

All of the statistical tests used bilateral analysis. $P \leqslant 0.05$ is considered to be statistically significance (excluding special conditions).

Description of quantitative indicators is used to calculate total cases, missing cases, average cases, standard deviation, minimum, maximum, median and the interquartile range.

Description of classification index is used in different groups of cases and percentage.

Full Analysis Set (FAS): this analysis includes all subjects who received any treatment and provided useful value after the baseline stage for analysis. It also includes violators of the research scheme and subjects with incomplete data who left the trial.

Per Protocol Set (PPS): this analysis includes all subjects who completed the research and complied with the scheme without any serious errors. It also includes subjects who quit the trial because of ineffective treatment.

Safety Analysis Set (SAS): this analysis set includes all subjects who enrolled in the trial, received at least one treatment and was used for safety evaluation. Safety information records from all subjects were evaluated, including adverse events and the results of lab examinations.

6. Adverse Event

6.1 definition

Adverse Event : An AE is defined as any untoward medical occurrence, regardless of its relationship to the study device (study suture) or the study procedure. An untoward medical occurrence includes any new, undesirable medical experience or worsening of a pre-existing condition, which occurs at any point from the surgery to Final Visit.

Serious Adverse Event: A Serious Adverse Event (SAE) is any AE that:

- led to a death,
- led to a serious deterioration in the health of the subject that either resulted in:

- a congenital deformity or abnormality;
- a life-threatening illness or injury;
- a permanent impairment of a body structure or a body function;
- in-patient hospitalization or prolongation of existing hospitalization;
- medical or surgical intervention to prevent life-threatening illness or injury; or permanent impairment of a body structure or a body function.

Relationship of Adverse Events: It is the Investigator’s responsibility to assess the relationship of an AE to the study procedure and study device.

The following guidelines should be used in determining the relationship of an adverse event

to the study device, study procedure, or other causality:

- NOT RELATED: The event is due to extraneous causes.
- POSSIBLY RELATED: The event is unlikely associated, but cannot be ruled out with certainty.
- PROBABLY RELATED: The event is likely associated, but another cause cannot be ruled out with certainty.
- DEFINITELY RELATED: The event is associated with a high degree of certainty; or
- UNKNOWN: The event cannot be defined by the categories listed above.

6.2 Reporting adverse event and management: The adverse event is reported from the start of signing the informed consent to the end of the study of subjects. All adverse events should be followed up, until the adverse event is resolved, stable or the study is completed. Investigator will ensure to provide the sufficient treatment for any adverse event of any subjects. The investigator will report the serious adverse events occurred in the study and the device defects that may cause serious adverse event to the regulatory authorities at every level according to the requirements of laws and regulations. Any study-device-related SAEs will be reported to Medtronic by the investigator.

7. Publication plan

The study outcome is expected to be published on the: Journal of Parkinsonism and related diseases, Brain Stimulation, J Neurosurgery, or Movement Disorders.

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