A randomized double-blind prospective cross-over study on chronic effect of low frequency 60Hz stimulation on aspiration, freezing of gait and other axial and motor symptoms in Parkinson patients with STN DBS and freezing of gait at 130Hz and on the potential carry-over effect of different conditions (60Hz vs 130Hz vs DBS off)

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NCT Number: NCT02549859

Date: 01JUL2015

Funded by: Michael J Fox Foundation to Tao Xie. The current study is basically an extension study of our previous one (IRB 13-0566; Effects of the stimulation frequency of STN DBS on swallowing function in patients with Parkinson's disease) but with a longer follow-up period (at least 6 months) in more patients and a full evaluation in each visit of maximum 2 visits in some patients.

Study Period: August 15, 2015-March 15, 2017

Background & Rationale:

Subthalamic nucleus (STN) deep brain stimulation (DBS) improves the levodopa responsive cardinal symptoms (bradykinesia, rigidity and resting tremor), and reduces motor fluctuation and dyskinesia in patients with Parkinson's disease (PD) [1-5]. However, DBS was less effective at improving the axial symptoms (postural instability, gait disorders such as freezing of gait (FOG), speech and swallowing dysfunction), or even could make them worse over the course of 2-5 years after STN DBS [6-15]. Worth noting that the DBS stimulation frequency used in these studies was the traditionally high frequency of 130-185Hz.

Seeking an effective treatment on the axial symptoms is critical, as the axial symptoms are common in advanced PD patients, with subsequent falls and aspiration pneumonia being the

major causes of mobility and morbidity in PD. Pharmacological treatment is hardly effective in treating axial symptoms.

Over the past several years, there were studies suggesting that, compared to the traditionally high frequency stimulation of 130Hz, low frequency stimulation of 60Hz improves the FOG [16-19] and dysarthria [15, 19]. The beneficial effect was not necessarily only seen in chronically stimulated patients with disease progression, as it was also seen in patients with newly activated bilateral STN DBS [19].

More recently, we for the first time further studied the effect of the 60Hz stimulation on another axial symptom, dysphagia, in patients on bilateral STN DBS who had medication refractory FOG at 130Hz [20] (supported by MJFF under Rapid Response Innovation Award program to TX). We found that 60Hz stimulation, compared to the traditional 130Hz, decreased not only the aspiration frequency by modified barium swallowing (MBS) test and swallowing difficulty by swallowing questionnaire, but also the medication refractory FOG (by SWS stand-walk-sit test and FOG questionnaire), and axial symptom subscore and general parkinsonism motor symptom UPDRS-III score [20]. The beneficial effect of the 60Hz stimulation persisted during the 6-week study period, except that one of the patients had to switch back to 130Hz stimulation in 3 weeks due to worsening of the hand tremor.

The effect of the 60Hz stimulation on STN DBS patients without FOG at 130Hz stimulation was also studied, with significant improvement on axial and motor symptoms in 14 patients in an acute phase study [21], and mild improvement on gait without improvement on other motor symptoms in another study [22], suggesting the overall benefit of the 60Hz stimulation, though may not as great as seen in these with FOG at 130Hz stimulation.

However, it remains unknown whether the beneficial effect of the 60Hz stimulation would persist on extended chronic stimulation beyond the 6-week period, and whether there is carry-over effect during the study across different test conditions of 30-minute apart in our previous study [20]. Clarifying these two questions is crucial for the clinical application of the 60Hz stimulation chronically and confidently to treat the medication refractory axial symptoms.

So far, there was only one study showing persistent benefit of the 60Hz stimulation on FOG in 85% of the 13 patients with bilateral STN DBS at medication off state following up in 8 months[16]. There were two other studies challenging the chronic benefit of the low frequency stimulation [23-24]. One of them reported an improvement in the gait immediately after switching the 130Hz stimulation to 80Hz at medication on state in 11 STN DBS patents, but the benefit only lasted for less than 1 month [23]. The other one reported no benefit at 80Hz stimulation compared to 130Hz in axial symptoms following for almost 4 months (111.5 days on average) in 45 patients [24]. Worth noting that none of these two studies was really studying FOG, as one of them had no FOG on exam and the other one was not assessing FOG. Besides, these two studies used 80Hz, instead 60Hz, stimulation. None of them studied swallowing function either.

According to our continuous observation since we published our study [20], all of our 5 out of 7 patients who was on 60Hz simulation for 6-week study period remains on 60Hz since then for

its benefit on axial symptoms including FOG, over the period of up to 14 months follow up so far, which indicates a sustained chronic benefits. The 2 of the 7 patients were not on 60Hz stimulation after the previous study because of slightly worsening of tremor in 1 of them, and skin infection after the battery replacement (unrelated to the study) in another one. A formal randomized double blind prospective cross-over study on the chronic benefit of the 60Hz stimulation over an extended period of at least 6 months, corrected for the potential carry-over effects on this crossover study (DBS off, 60Hz or 130Hz while all at medication on state) at the acute (visit 1) and chronic phase (visit 2), is needed to enhance the quality of the study, the evidence level and the level of the recommendation in clinical applications to treat the axial symptoms which are refractory to usual DBS setting and medications with high morbidity and mortality of the PD.

All Parkinson's disease patients who have had aspiration pneumonia within the past one month before the test will be excluded.

This study is basically an extension study of our previous one (IRB 13-0566; Effects of the stimulation frequency of STN DBS on swallowing function in patients with Parkinson's disease, with publication in reference 20) but with a longer follow-up period (at least 6 months) in more patients and a full evaluation in each visit of maximum 2 visits in some patients.

Hypothesis:

The 60Hz stimulation would have persistent benefit in reducing the aspiration, FOG, other axial and motor symptoms in PD patients with bilateral STN DBS and medication refractory FOG at 130Hz stimulation over an extended period of at least months, even corrected for the potential carry-over effects between different test conditions.

Innovation:

This would be the first study on the chronic effect of the 60Hz stimulation on the dysphagia, FOG and other axial and motor symptoms in PD with bilateral STN DBS with medication refractory FOG at 130Hz stimulation.

Significance:

This study will provide a high evidence level and clinical recommendation on the chronic effect of the 60Hz stimulation on the treatment of the axial symptoms, particularly dysphagia and FOG, which are refractory to usual DBS setting and medications and associated with high morbidity and mortality in PD.

Aims:

Aim 1a: A study on the chronic effect (at least 6 months) of 60Hz stimulation on axial symptoms, including swallowing function and FOG, and parkinsonism to see whether the beneficial effect of 60Hz stimulation compared to 130Hz as revealed in our previous study [20], could be sustained in PD patients with bilateral STN DBS with medication refractory FOG at 130Hz.

Aim 1b: This study would also clarify the potential carry-over effect on stimulation (DBS 60Hz, DBS 130Hz, and DBS off, 30 min apart) on acute and chronic phase of the study to

enhance the quality of the study, and the level of evidence and recommendation in clinical applications.

Approach:

Towards that aim, we will add 12 patients with medication refractory FOG at 130Hz of bilateral STN stimulation at medication on state for two visits of at least 6-months apart. We will plan to have 14 patients enrolled for visit 1, as 2 of them might drop off (or being unable to be on 60Hz due to worsening tremor) before visit 2 (estimated based on our previous study that 1 out of 7 patients could not be on 60Hz due to worsening tremor [20]). The previous 6 study patients remaining on 60Hz stimulation after the completion of our previous study will be assessed again at visit 2 at least 12 months after the initial visit 1 once we get the IRB approval here.

We will then combine the data from these 14 newly added patients with the previous 7 patients at visit 1 to make 21 patients to complete the visit 1, and 18-20 (12 to 14 newly added patients plus previous 6) patients to complete a longer interval visit 2 of at least 6 months apart.

As our previous study[20], it will still be a randomized double-blind prospective cross-over study with medication on state but with 6-8 patients on each group of starting condition (60Hz vs 130Hz vs DBS off, 30 min apart) to allow us analyze the chronic effect and potential carry-over effect of stimulation between different conditions to increase the level of evidence, with 80% power to detect at least 25% difference at two-tail α level of 0.05, as estimated before [20]. Aspiration frequency on MBS, difficulty in swallowing on questionnaire, FOG in SWS test and questionnaire, and axial subscore and UPDRS-III score will all be assessed accordingly under each DBS conditions as we did in our previous study [20], at both visit 1 and visit 2 of at least 6 months apart. The study will be finished in 2 years.

Specifically, all the study patients will sign a written consent after the IEB approval. The study will be conducted at the Parkinson's Disease and Movement Disorder Center of Department of Neurology, Department of Radiology, Speech and Swallowing Section of Department of Surgery, and Center for Research Informatics at the University of Chicago from August 15, 2015 to March 15, 2017. Advanced PD patients with bilateral STN DBS placement and medication-refractory FOG at routinely used 130-Hz stimulation will be enrolled. The demographics of patients, such as gender, age at the study, disease duration, duration on bilateral STN DBS, and their Parkinson medications, electrode position and active contact positions and settings will all be recorded.

During visit, each patient will receive 3 routine modified barium swallow (MBS) studies in a single day under 3 different DBS frequency conditions (bilateral DBS 130 Hz, DBS 60 Hz, or DBS off) with their usual DBS voltage, pulse width, contact setting, and parkinsonian medication-on state regardless of the study stimulation frequency used. The study will be performed in a randomized and double-blind manner. The order of the DBS conditions will be assigned by the neurologist who will randomly pick up one of the 3 folded sheets with different conditions written on them and program the DBS accordingly, but will not be allowed to participate in any rating or evaluation. Neither the patients, nor the clinical rater, the pathologists for speech and swallowing, or the radiologist is aware of the DBS stimulation frequency condition. A single certified rater will rate all of the clinical scales and questionnaires, and a single swallowing team will conduct all MBS studies and the Penetration-

Aspiration Scale ratings [25] to ensure consistency and quality of the evaluation. The MBS protocol consists of a standardized videofluorographic recording of oropharyngeal swallow in lateral and anterior-posterior views, and the anterior-posterior views. The subjects will be given radiopaque liquid, pureed contrast material, and solids coated in barium paste. The examinations will be recorded on the TIMS-DICOM digital medical recording system at high resolution of 30 frames per second. Frame-by-frame analysis will be used to evaluate oral, pharyngeal, laryngeal, and cricopharyngeal function. For the purposes of this study, special attention will be given to aspiration. Laryngeal penetration and aspiration events will be assessed using the Penetration-Aspiration Scale. The frequency of aspiration events will be calculated by adding the number of swallows within each DBS condition that generates a Penetration-Aspiration Scale. The swallowing questionnaire will be completed by each patient after the MBS study under each DBS condition[26]. The parkinsonian motor, axial, and tremor symptoms as reflected by the Unified Parkinson's Disease Rating Scale, Part III (UPDRS-III) score, axial subscore (including gait, stance, posture, postural stability, and speech), and tremor subscore, respectively, and the FOG as reflected by a FOG questionnaire score,27 and stand-walk-sit (SWS) test on FOG spell times and the time needed to finish the test (seconds) will also be assessed before the MBS study under each DBS condition. The patients will be on each DBS condition for at least 30 minutes before the study. The subjects will be video recorded while walking. The DBS condition producing the best gait function (least FOG, which was 60 Hz for all of our previous patients) will be continued for at least 6 months for the newly enrolled patients.

Analysis: Changes in measurements between the 60Hz and 130Hz will be analyzed using paired t-test, with swallowing function (objective MBS study and subjective swallowing questionnaire) and FOG (objective SWS study and subjective questionnaire) as primary outcomes, and the rest (UPDRS-III score, axial subscore and tremor subscore) as the secondary outcomes in both acute visit1 and chronic visit 2 phase. Changes between other clinically relevant DBS conditions, including 60Hz vs DBS off, 130Hz vs DBS off, and 60Hz vs 60Hz follow-up (for >8 months on average) will also be explored and similarly analyzed with Bonferroni correction. A two-tailed alpha level of 0.05 will be taken as statistically significant for the comparisons.

Foreseeable difficulty or complications:

We don't anticipate any difficulty in conducting this study, as we had a successful similar study before [20], with IRB approval (University of Chicago). Medication refractory tremor could offset the 60Hz use as the tremor could be worse compared to 130Hz. However, most of the patient with axial symptoms has less tremor, and medication refractory tremor is even less. In the past, we had only 1 out of 7 patients who could not be on 60Hz stimulation due to the worsening of the tremor [20]. No complication of aspiration pneumonia was found or reported before. The DBS condition used in the study will be the routine range of condition used in daily living without side effects. There is no alternative ways to conduct current study in order to get the important questions answered.

Pregnant woman, children or mentally retarded patients: None of them will be involved, as these advanced patients are all at the post-menopausal age. No children will be involved in

these advanced PD patient population. No mental retarded patient will be involved. All the patients will have the capacity to consent.

All study subjects will be paid $200 for their participation in each visit study.

Research Environments:

We have a good team to accomplish this study, consisted of PD and DBS specialists (TX, UJK, JB, PW), speech and swallowing specialist (JV and EM), functional neurosurgeon (PW), and biostatistician (WK). Dr. Xie is the PI of the previous acute phase of 6-week period study funded by MJFF resulting in an important publication in Neurology [20]. He has published 5 peer-reviewed papers on DBS as the first and corresponding author, with many other publications on PD and movement disorders. He is the Director of the DBS Program and the PD & Movement Disorder Clinic at the University of Chicago. Dr. UJ Kang is the internationally recognized PD and movement disorder specialist and the Chief of the Movement Disorder Section at Columbia University Medical Center. He will serve as the consultant in our study. Dr. Bernard is a movement disorder neurologist who will help the double blind operation of the study. Ms. Vigil and Ms. MacCracken are the speech and swallowing experts with Ms. MacCracken being the Chief of the Speech and Swallowing Section in Department of Surgery at University of Chicago. Dr. Warnke is the Director of the Stereotactic Functional Neurosurgery at the University of Chicago. Mr. W Kang is the experienced statistician who also did data analysis for our previous study [20].

Time Frame and Budget:

The study will be finished in 2 years. The total budget (direct cost) will be $ 145,000/year x 2 years = $290,000. Year 1: a) month 1–2: IRB and paper work; b) month 3- 6: finish visit 2 on the remaining 5 patients from previous study [20], who have been on 60Hz stimulation for up to 15 months by then; c) month 7-12: enroll the first 7 newly added patients and finish the visit 1 study on them. Year 2: a) month 1-6: enroll the remaining 7 newly added patients and finish the visit 1 study on them; b) month 7-12: finish the visit 2 on all the newly added 12 patients (2 of the 14 newly enrolled patients on visit 1 might have dropped at visit 2).

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