Changes in Optimal Stimulation Frequency with Time for Gait Disturbances in Patients with PD after STN-DBS—A Longitudinal Study

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Abstract

Aim: To assess the changes in frequency parameters of STN-DBS stimulation over 6 months required to optimize gait in PD patients. **Methods:** It's a single center, open label longitudinal study of PD patients after STN-DBS with gait disorders. Gait assessment using stand–walk–sit (SWS) test and freezing of gait (FOG) scores were done at baseline and after 6 months. Gait was assessed in five frequencies settings, that is, 60 Hz, 90 Hz, 130 Hz, 180 Hz and stimulation "OFF" during medication ON state. Voltage was maintained. **Results:** Fifteen post-deep brain stimulation (DBS) patients were included. Mean duration after surgery was 3.73 ± 2.82 years. In SWS and FOG at baseline, five patients have good response at 180 Hz frequency, five at 130 Hz, one at 90 Hz, two patients at 60 Hz, one both 60 and 90 Hz, and one at both 90 and 180 HZ. And after 6 months out of the 13 patients who were able to perform the test, four patients had good response at 180 Hz frequency, four at 130 Hz, two at 90 Hz, one each for 60 Hz and battery OFF state, and one for both 130 Hz and 180 Hz. At 6 months, four patients had good response at the same frequency as baseline, while 11 patients have change in frequency from baseline. **Conclusion:** Optimal frequency for gait varies in patients—both low and high frequency may be useful. Optimal frequency for improving gait changes over period of time. Regular assessment and changing frequency may improve gait after DBS.

Keywords: Deep brain stimulation, frequency, gait, subthalamic nucleus stimulation

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease with an estimated prevalence of 52.85/100000 in India.[1-3] This neurodegenerative syndrome is manifested by a combination of motor and non-motor symptoms.

Bradykinesia, tremor, and rigidity are the three cardinal motor features. A fourth feature, which occurs later in course of disease, is postural instability.[4] In addition, gait disturbances and freezing episodes (frequently resistant to optimal dopaminergic treatment) often appear in advanced Parkinson disease and are difficult to treat. Gait difficulty and postural instability are major contributors to disability in patients with PD.[5]

Over the past 20 years, deep brain stimulation (DBS) has become an important therapeutic option for PD patients with motor fluctuations and dyskinesias. DBS of bilateral subthalamic nuclei (STN) is common in India and causes significant improvement in rigidity, bradykinesia, and tremor and increases "ON" time without dyskinesias.[6]

Till date, the effect of STN stimulation on freezing of gait (FOG) is unclear. This is due to various reasons. First, laboratory assessment of FOG during "ON" and "OFF" stimulation may not reflect FOG in daily life due to its unpredictable nature. Second, both improvement and worsening of FOG with bilateral STN-DBS have been reported depending on voltage/frequency stimulation settings and follow-up time. Third, as PD is a dynamic disease, the effects of STN-DBS on FOG are not constant over time.

Most studies have assessed using stimulation with lower frequencies (60 and 90 Hz) which seem to confer some benefit to patients with FOG. But the benefits may wane with time. We had previously reported that a more individualistic approach is beneficial with different frequencies for different patients.[7]

But it was not clear if the frequency chosen persisted to show a similar benefit over time. In this study, we assessed if the frequency chosen at baseline showed a similar benefit even at 6 months follow-up.

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Aim

The aim of the present study is to assess the changes in frequency parameters of STN-DBS stimulation over 6 months required to optimize gait in PD patients.

Methods

This is an open label longitudinal interventional study, undertaken in a Neurology Department of a Tertiary Care Hospital, where PD patients are seen and DBS surgeries are done on regular basis. Ethical committee approval was taken from the institute (Ethics approval number 642/2018). Informed written consent was taken from patients.

Patient characteristics

Inclusion criteria

1. PD patients who underwent bilateral STN-DBS.
2. Patients with complaints of gait problems.
3. Patients who had meaningful response (improvement in medication "OFF" score by at least five points on the UPDRS-III with DBS stimulation).

Exclusion criteria

1. Post-DBS patients who were unable to walk.
2. Post-DBS patients with surgical complications, for example, lead removed due to infection and malfunction.
3. Medical co-morbidities with poor medical health, for example, severe osteoarthritis of knee, and diabetic neuropathy.
4. Post-DBS patients who were not willing/unable to come for follow-up.

All patients included in the study were diagnosed as PD by a movement disorder specialist at our hospital and were considered for STN-DBS based on CAPSIT-PD protocol. All patients were operated by a qualified neurosurgeon.

Stereotactic surgery was performed using CRW frame under MRI guidance with intraoperative five-channel microelectrode recording. Final lead placement in bilateral subthalamic nuclei was based on MER recording and intra-operative stimulation. Post-operative MRI was performed in all. Lead was determined by post-OP MRI and clinical assessment. Monopolar stimulation was performed using the contact within the STN as negative and the case being positive. All were managed post-operatively on a combination of dopamine replacement therapy and DBS. All patients underwent neurological evaluation using UPDRS part III for motor evaluation before surgery, and score was documented.

Gait assessment

Patients were assessed during medication "ON" state. The tests were performed at baseline and after 6 months. STN-DBS parameters were changed using a handheld device that communicates wirelessly with the implantable pulse generator. Every patient was assessed using four frequency settings, that is, 60 Hz, 90 Hz, 130 Hz, and 180 Hz and device "OFF" state. All patients received monopolar stimulation with constant pulse width (60 µsec) and constant voltage during the assessments. A time gap of 20 minutes was given after change of each frequency, each patient underwent the following tests—the Stand–Walk–Sit (SWS) and freezing of gait (FOG) scoring. (Figure 1 shows the flowchart of methodology) Video of entire procedure was taken, and parameters were calculated from videos.

1. **The Stand–Walk–Sit (SWS):**

To get up from chair and walk 5-meter distance, turn and come back and sit. Number of freezing episodes, completion time, and the number of steps required were recorded in proforma.[8]

2. **FOG scoring:**

This test was performed in a standardized area of length 5 meter in corridor with an open doorway at the end of it. A 2-meter diameter circle was drawn midway of 5-meter distance, and patient was asked to walk straight up to the beginning of circle then to walk clockwise and then anti-clockwise, each once around the circle, after that continue to walk rest of 5 meters, go through the doorway, and turn and come back to sit. Second time, the same procedure was repeated carrying some object (book) with both hands. Third time, the procedure was done carrying an object along with mental arithmetic (performing serial subtraction of 7 from 100). Freezing of gait scoring was performed in all three states.

These assessments were done at baseline (0 months) and repeated after 6 months.

DBS stimulation from baseline to 6 months follow-up: Once the patients were optimized on the rate (based on the best

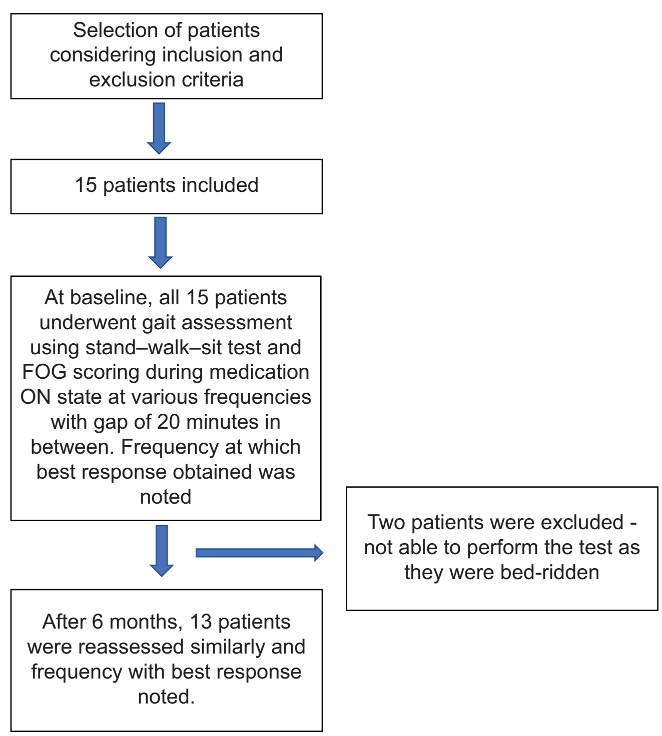

Figure 1: Flowchart depicting the methodology

response at baseline), all patients were continued on monopolar stimulation with same rate, standard pulse width of 60 µsec, and modifications in voltage, depending on the need of the patient.

Statistical analyses

Wilcoxon ranked sum test was used to study the differences between means. All tests were two-sided, and *P* value of < 0.05 was considered significant.

Results and Observations

Fifteen post-DBS patients were included in the study, and out of which 13 are male and 02 are female. Average mean age was 58.47 ± 11.35 years. Demographic details of patients are given in Table 1. Mean UPDRS OFF and ON scores at baseline were 49.93 and 13.20, respectively, and after six months, mean scores were 21.59 and 10.32, respectively.

Gait parameters

Best response

We determined the frequency, which leads to the best response in each patient. The best response was defined as that with the lowest completion time on Stand–Walk–Sit (SWS) test. If two frequencies had the same completion time, a lower number of steps were considered. We analyzed the best response on FOG score independently. If there was a discrepancy between the two, response on FOG score was used to treat the patient.

Stand–Walk–Sit test (SWS)

Baseline response at 0 months

There was no uniform frequency. Best response differed among the patients and is given in Table 2. In SWS test, five patients have good response at 180 Hz frequency, five patients have good response at 130 Hz, one patient at 90 Hz, and two patients at 60 Hz. Patient "10" had good response at both 60 and 90 Hz and Patient no "11" at both 90 and 180 HZ.

Response at 6 months

Patients who were analyzed at baseline were reviewed for analysis after a minimum period of 6 months. Thirteen patients were able to perform the test after 6 months, and two patients were not able to perform the test as they were bed-ridden (Patient No. 9 and 15). As was noted at baseline, there was no uniform frequency in patients after 6 months and best response differed among the patients [Table 3].

Out of the 13 patients who were able to perform the test at 6 months, four patients had good response at 180 Hz frequency, four had good response at 130 Hz, two patients have good response at 90 Hz frequency, and one each for 60 Hz frequency and battery OFF state. Patient No. 12 had good response in two frequencies that is 130 Hz and 180 Hz.

Comparing the stimulation frequencies at baseline and follow-up, among the 13 patients, four patients had same frequency at both times and all other had change in frequency after 6 months. Five patients went from higher to lower frequencies, three went from lower to higher frequencies, and one patient had dual response and felt better with higher and lower frequencies when compared to baseline. [Figure 2]

Freezing of gait score (FOG)

Similar results were seen with FOG scores. The frequencies with best response were same when FOG scores were taken while walking and during dual tasking.

At baseline, six patients had best response with 180 Hz stimulation, three with 130 Hz, and two each at 90 Hz and 60 Hz frequencies. Patient no. 10 had good response at 60 and 90 Hz, while Patient no. 11 had good response at 180 and 90 Hz. [Table 4].

At 6 months follow-up, frequencies with best response in FOG and dual-task assessments were similar.

Table 1: Demographic details of patients in the study

S. NO	Age (years)	Sex	Duration of Disease (years)	Time to Assessment after DBS (years)	Updrs off	Updrs on
1	55	M	6	2	65	20
2	64	F	9	3	44	14
3	67	M	10	1	57	16
4	61	M	6	3	28	8
5	64	M	7	2	54	12
6	34	M	14	1	74	13
7	75	F	6	1	47	16
8	59	M	13	5	74	25
9	55	M	19	11	46	10
10	51	M	17	6	24	4
11	46	M	17	8	35	6
12	73	M	9	2	56	15
13	40	M	8	3	54	14
14	68	M	13	2	43	8
15	65	M	11	6	48	17
SD	11.35		4.18	2.82	14.13	5.31
Mean	58.47		11.00	3.73	49.93	13.20

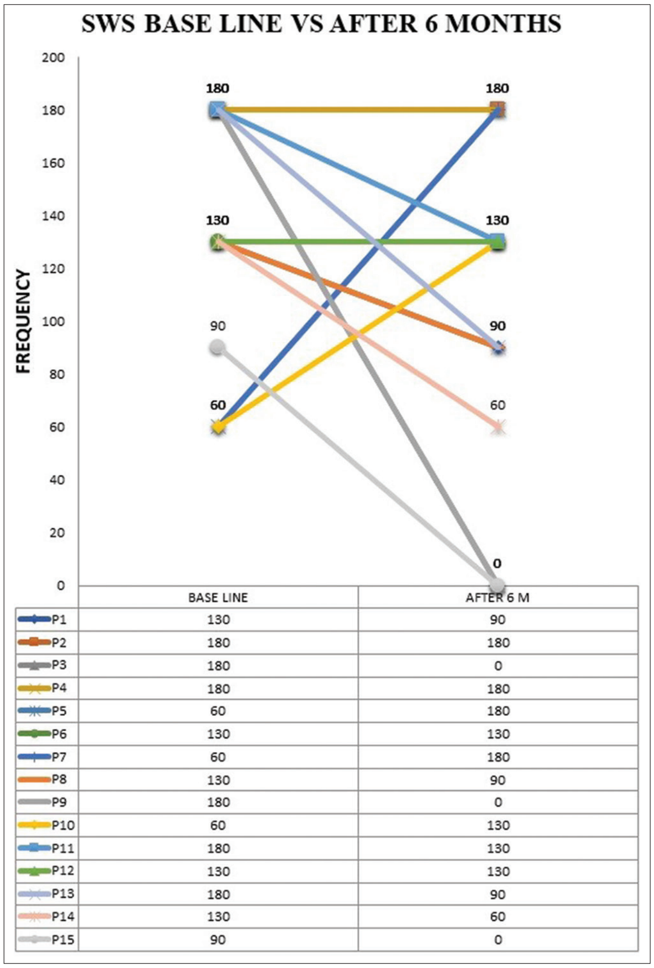

Figure 2: Comparison of optimal stimulation parameters in stand–walk–sit test at baseline and after 6 months

At 6 months of baseline study [Table 5], four patients had good scores at 180 Hz, two had at 130 Hz, two had at 90 Hz, and two had at 60 Hz frequencies. Patient no. 3 had good response in battery OFF state, Patient no. 10 had good response at 90 and 130 Hz, and Patient no. 12 had good response at 180 and 130 Hz. Two patients were bed-ridden and were unable to perform the test (Patient no. 9 and 15) [Figures 3 and 4].

We compared the best frequency at baseline and at 6 months for each individual on both SWS and FOG scores. Four patients (26.7%) had best response at same frequency in both SWS and FOG after 6 months. The rest required a change in frequency for optimizing gait.

Comparison of gait parameters

We compared the best responses at baseline and 6 months and found no significant difference on Wilcoxon signed rank test.

We also looked at the voltage delivered with the neurostimulator. There was no significant change in voltage comparing baseline and 6 months follow up. (Left lead was *P* value: 0.8390 and right lead *P* value: 0.4827).

Table 2: Frequencies at which patients have best response in SWS test 0 months (baseline)

SWS Baseline (0 month)						
Best Frequency	**Patients Serial No.**					
OFF						
60	5	7	10			
90	10	11	15			
130	1	6	8	12	14	
180	2	3	4	9	11	13

Table 3: Frequencies at which patients have best response in SWS test after 6 months of baseline

SWS After 6 months					
Best Frequency	**Patients Serial No.**				
OFF	3				
60	14				
90	1	8			
130	6	10	11	12	13
180	2	4	5	7	12

Table 4: Frequencies at which patients have best response in FOG and dual-task scores test at baseline

FOG and Dual-task Scores Baseline							
Best Frequency	**Patients Serial No.**						
OFF							
60	5	7	10				
90	8	10	11	15			
130	6	12	14				
180	1	2	3	4	9	11	13

Table 5: Frequencies at which patients have best response in FOG and dual-task scores after 6 months

FOG and Dual-task Scores after 6 months					
Best Frequency	**Patients Serial No.**				
OFF	3				
60	8	14			
90	1	10	13		
130	6	10	11	12	
180	2	4	5	7	12

Discussion

The effect of DBS on gait has been unclear in most studies with a possible partial improvement after surgery. A recent review looked at the effects of DBS on gait parameters and concluded that the existing data suggest that both STN and GPi-DBS improve gait parameters and quiet standing postural control in PD patients, but have no effect or may even aggravate dynamic postural control, in particular with STN-DBS.[9] Few studies also looked at DBS of the pedunculopontine nucleus (PPN) for gait disturbances and have shown that DBS of the PPN

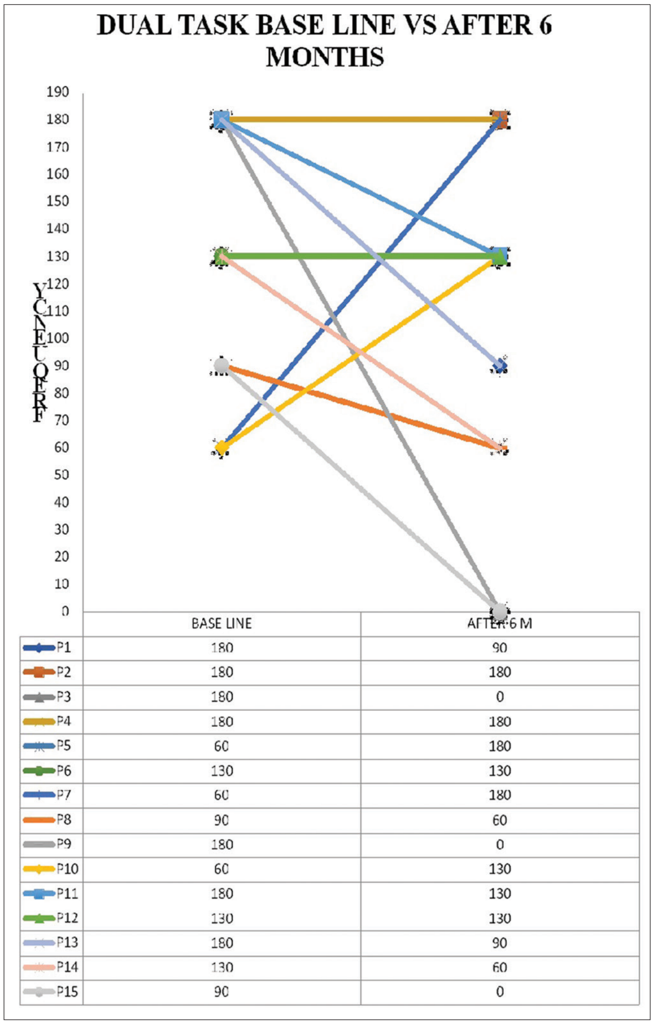

Figure 3: Comparison of optimal stimulation parameters in dual task at baseline and after 6 months

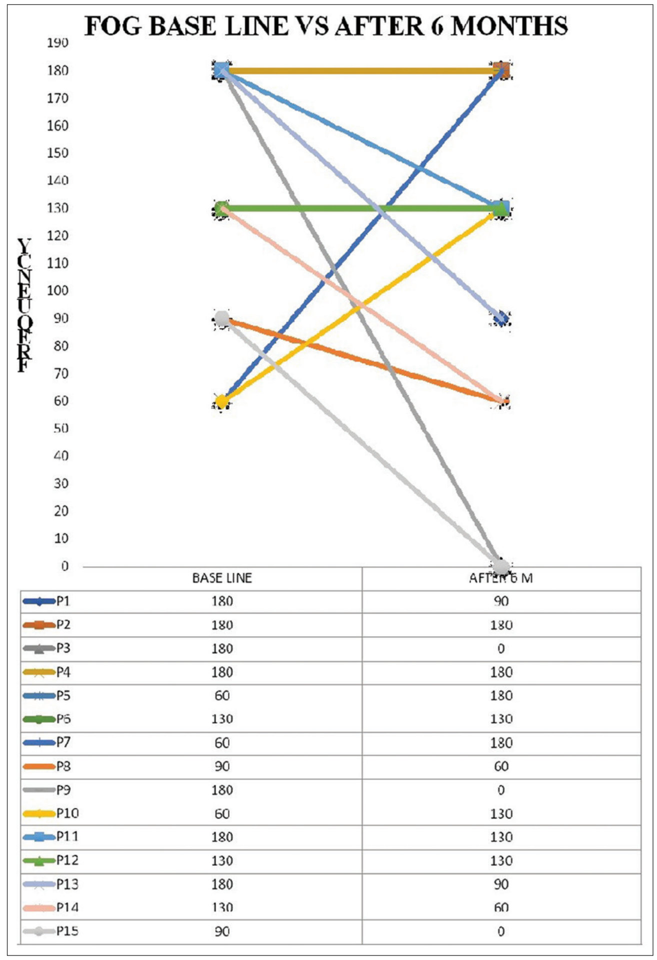

Figure 4: Comparison of optimal stimulation parameters of FOG scores at baseline and after 6 months

has no effect on gait parameters but may improve postural adjustments and gait postural control.[10]

FOG refers to the transient inability to initiate effective stepping without any apparent cause other than Parkinsonism or high-level gait disorders. The episode is commonly experienced during turning and step initiation, as well as when faced with spatial constraint, stress, and distraction.[11] While focused attention and external stimuli can overcome the episode, the pathogenesis of FOG remains unclear. Injuries to the nervous system at various levels can lead to FOG in PD patients, resulting from acute neural network overload associated with neural decomposition under motor conflicts, cognitive, or emotional stimuli.[12,13]

Research suggests that the loss of functional connectivity of the STN-SMA circuit leads to the loss of the ability to inhibit competitive activity and initiate the right motion, causing FOG.[14] Abnormalities in the functional connectivity of PPN and microstructural anomalies of the subcortical region are also relevant to FOG, with PPN playing a key role in its pathogenesis and serving as an important therapeutic target for DBS.[15]

Vandenbossche *et al*.[16] proposed the cognitive model conceptualizes FOG as a specific impairment of conflict resolution and deterioration of executive functions, with two tracks—a direct route requiring automatic responses regulated by the basal ganglia and an indirect route eliciting a controlled response regulated by frontal cortical areas. STN-DBS can modify these two routes via different targets, improving cognitive functions and regulating automaticity and controlled processes. Also because of close interconnections among the cerebral cortex, basal ganglia, and PPN, PPN-DBS is able to regulate both direct and indirect routes.[7]

Given the mutual interaction between FOG and cognitive function, it can be inferred that the improvement of FOG may be related to cognitive improvement. Niu *et al*.'s[17] study, besides FOG, global cognitive assessment of neuropsychological function was also performed with the Mattis Dementia Rating Scale. They demonstrated bilateral STN-DBS improved FOG as well as neuropsychological function at 6 and 12 months after surgery, suggesting the improvement in neuropsychological function may be an important mechanism underlying the therapeutic effect of STN-DBS on FOG.

Combined stimulation of PPN plus STN, PPN plus GPi, and STN plus SNr may achieve a better effect in improving various symptoms of FOG. However, the efficacy of STN-DBS in FOG remains a topic of debate, with the different stimulation frequencies of STN-DBS having a significant impact on the treatment's effect.

There has been a move toward changing frequencies for improvement in gait, and most studies have assessed lower frequencies which seem to confer some benefit to the patients in their gait.

Moreau *et al*. (2008)[18] in his study of 13 patients who had undergone STN-DBS within 5 years of surgery showed that acutely, the number of freezing episodes was significantly lower at the 60-Hz "high voltage/equivalent energy" and higher at the 130 Hz/high voltage than for "OFF stimulation." In the study, they used higher voltage at lower frequencies to compensate for the overall energy and found that at 60 Hz high voltages equivalent energy led to the greatest improvement in all aspects of SWS test and FOG scores. During the follow-up of 8 months, two patients switched back to High frequency stimulation (HFS) due to worsening of tremor.

Hana Brozova *et al*. (2009)[19] tried 60 Hz in nine of his post-DBS patients who were having speech and gait disturbances on high frequencies. ON medication UPDRS scores were collected 8–12 weeks after switching to 60 Hz and compared to ON medication scores obtained at higher stimulation frequencies. Significant average improvements were observed for the UPDRS-II subscale (3.9 points; $P < 0.05$), UPDRS-II subitems relative to speech, falling, and walking ($p < 0.05$), and UPDRS-III subitems relative to speech and gait ($p < 0.05$). An average voltage increase of 1.3 volts (range 0.7–2.5) was required bilaterally in seven patients for beneficial maintenance of other PD symptoms.

Valeria Ricchi etal (2012) in his study evaluated the effect of 80 Hz stimulation on gait in STN-DBS treated PD patients and followed them at 1, 5, and 15 months and maintained equivalent total electric energy delivered (TEED). He noted a significant improvement of gait (SWS test) which was evident immediately after switching the stimulation frequency to 80 Hz, with no deterioration of PD segmental symptoms in 11 patients tested. In three patients, the frequency had to be shifted back to 130 Hz after 1 month due to incomplete control of motor symptoms, rest eight patients were continued on 80 Hz up to 15 months. They concluded that 80 HZ may have immediate effect on gait but may not be maintained over a long period of time.[20]

Tao Xie *et al.* (2015)[21] assessed seven patients and showed that compared with the routine 130 Hz, the 60-Hz stimulation significantly improved swallowing function, FOG, and axial and Parkinsonian symptoms in patients with PD treated with bilateral STN-DBS, which persisted over the 6-week study period.

Hui Ming Khoo *et al.* (2014)[22] conducted a randomized study comparing 60 Hz and 130 Hz and showed that 60 Hz provided superior efficacy over 130 Hz in improving the total unified Parkinson's disease rating scale motor score ($P < 0.001$) and the akinesia ($P < 0.011$) and axial motor signs ($P < 0.012$) sub-scores without compromising the therapeutic effect on tremor and rigidity. The optimized stimulation parameters with 60 Hz significantly reduced the time and number of steps required to complete the 10-meter walk. They found that optimized stimulation with 60 Hz was not superior for improving postural stability. However, they concluded that with improvement in other gait parameters, it may be potentially beneficial for reducing the risk of falling in patients with advanced PD.

On the other hand, Sidiropoulos *et al*.[23] studied 45 PD patients with DBS at 115.5 days after switch from HFS (135–185 Hz) to LFS (39 to 80 Hz and 6 to 60 Hz) at medication ON state without TEED maintained and found no significant improvement in UPDRS III, axial, and gait sub-scores. There are very few studies assessing various frequencies for improvement in gait and reassessing the patients on long-term follow-up.[24]

In our study, we kept the voltage constant and studied different frequencies on the gait parameters. As most patients are functionally active in their "DBS ON and medication ON state," we assessed our patients in medication ON state at baseline and after 6 months.

We attempted to assess the optimal frequency for each patient in regard to their gait at baseline and at gap of 6 months follow-up. Our results did not favor a single frequency but show marked variations in the best frequencies ranging from 60 Hz to 180 Hz.

Even individually, the optimal frequency did not stay constant in majority of patients and changed over 6 months. This suggests a constant dynamic modulation within the brain stem. Whether these changes are induced by the STN stimulation or by the disease process itself requires further analysis in the future.

We assessed the gait by SWS and FOG (scores with and without dual tasking) and did not find any difference in the best frequencies for gait with a concordance achieved over the tests.

In our experience, patients at the time of examination did not have any problems with reduction in overall energies with lower frequencies or higher energies with higher frequencies as we kept the voltage and pulse width constant. Further as the spread of the current depends primarily on the voltage which was kept constant, the change can be attributed to the stimulation effects on the STN itself and not to the surrounding structures. This also confirms that the benefit is definitely due to the frequency change and not just a sequalae of change in overall energies.

In our limited experience, we did not find any distinguishing features between responders at various frequencies among demographic and disease parameters (no significant difference in age of patient, disease duration, pre-DBS UPDRS score, voltage being used). This may be due to small numbers or other parameters which are not included in this study.

Our study is one of the few studies which has analyzed the effect of the various frequencies in DBS stimulation on gait over a long follow-up. It is a single center study with objective assessment by a single rater, thus negating any inter-rater variability.

Limitations of the study

1) We studied all patients in medication ON state and hence evaluated the gait at the best period in the patient, and hence, the results may differ in the medication "OFF" state. 2) We only stimulated the STN and did not assess stimulation of substantia nigra (may be beneficial) 3. The exact location of the lead in STN was not analyzed, and this may contribute to the gait changes. 3) We kept the frequency setting for only 20 minutes before testing, variable latencies of response after changing the frequency, may influence the gait. 4) We kept the amplitude and the pulse width of stimulation constant for each patient, and hence, some improvement may be due to change in the power of the current. 5) In the study, we did not assess other clinical features and disabling symptoms, thus cannot estimate the overall impact on functional status of the patient.

Conclusion

Our study has clearly shown that optimization of frequency setting for each patient can improve gait and that each patient may have a different optimal frequency and the frequency which is best for the patient changes constantly over period of time and has to be monitored regularly for the benefit of patient. Both higher and lower frequencies may be beneficial and every PD patient with gait abnormality should be evaluated for best frequency regularly on timely basis.

Ethical compliance statement

Approval of an institution review board was taken for this work (Ethics approval number 642/2018). Verbal and written consent was obtained from the patients for the publication of this study. We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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