Original Article

The Effect of Dual Tasking and Deep Brain Stimulation Frequency Parameters on Gait in Advanced Parkinson's Disease

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Abstract

Objective: To study the effect of dual tasking and deep brain stimulation frequency parameters on gait in advanced Parkinson's disease **Materials and Methods:** This is an open label interventional study evaluating 40 post STN-DBS patients with gait disturbances. All patients were diagnosed as PD by a movement disorder specialist using the United Kingdom Parkinson's Disease Society Brain Bank (UKPDSBB) criteria. Patients underwent bilateral subthalamic deep brain stimulation by a qualified neurosurgeon. Patients were managed on a combination of dopamine replacement therapy as well as deep brain stimulation. Patients were assessed by stand walk sit (SWS) test for a 5 meter distance and FOG scoring during medication 'ON' state and device "ON" state, at four frequencies 180, 130, 90, 60 HZ and device "OFF" state. **Results:** Out of 40 patients, 38 patients showed a significant improvement in gait at a single frequency (best response frequency) which is different for each patient. The mean FOG score showed significant improvement at all stimulation frequencies when compared to OFF stimulation ($P < 0.05$). The mean number of steps was 18.9 at best response frequency and 21.48 at 130 Hz ($P < 0.0001$). Number of freezing episodes also were significantly less with best frequency when compared to 130 Hz stimulation (0.28 and 0.65 respectively, ($P < 0.0001$). The mean FOG score was 6.45 at best frequency and 9.48 at 130 Hz ($P < 0.0001$). Mean Dual tasking score was 3.53 at best frequency and 5.15 at 130 Hz ($P < 0.0002$). **Conclusion:** Optimization of frequency setting for each patient can improve gait and that each patient may have a different optimal frequency.

Keywords: Dual tasking, deep brain stimulation, gait, Parkinson's disease

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease worldwide manifested by a combination of motor and nonmotor symptoms. The prevalence of PD in India is 52.85/100,000 and can cause significant morbidity.[1]

Deep brain stimulation (DBS) is an effective treatment modality for patients with PD who have motor fluctuations and dyskinesia. While DBS is shown to improve the core symptoms like bradykinesia, rigidity, and tremor, high-frequency subthalamic nucleus deep brain stimulation (STN-DBS) has been shown to be effective for up to 10 years of surgery in controlling the segmental symptoms.[2]

Severe gait disturbances and freezing episodes (frequently resistant to optimal dopaminergic treatment) often appear in advanced PD. However, the effect of DBS on freezing of gait (FOG) in PD has not been studied adequately. The reason being the problems in the laboratory assessment of FOG in ON and OFF stimulation states due to its unpredictable nature and that it may not reflect FOG in daily life. Previous studies have shown contradictory results. Both improvement and worsening of FOG have been reported depending on voltage/frequency of stimulation and follow-up time. However, the effects of STN-DBS on FOG have never been compared with continued best medical treatment (BMT) in a controlled design.[3] Modulating various parameters during stimulation has shown varied results on control of different symptoms.

Excessive synchronous neuronal activity of beta frequency (13–30 Hz) is reported due to the hypodopaminergic state in PD. Dopamine replacement reduces beta oscillations. DBS influences the pattern of neuronal firing by regularizing burst activity and suppressing synchronized oscillations. It also reduces the strength of cortical striatal phase—amplitude coupling. Although high-frequency stimulation at 130–185 Hz suppressed beta oscillations, the therapeutic mechanisms of DBS are still unclear.[4,5]

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Table 1: Scoring system used in the present study[11]

Observed leg movement	No festination and/or FOG	Festination	FOG: Trembling-in-place and/or total akinesia	FOG: Abortion of task/situation or need for external help and/or cue
Score	0	1	2	3

Table 2: Score sheet based on Table 1[11]

	Task	Situation	Score
1	Walking	Start	
2		Turn clockwise	
3		Turn counterclockwise	
4		Passage of doorway	
5	Carrying	Start	
6		Turn clockwise	
7		Turn counterclockwise	
8		Passage of doorway	
9	Carrying & calculation	Start	
10		Turn clockwise	
11		Turn counterclockwise	
12		Passage of doorway	
Total score (sum of item scores 1-12)			

In addition, high-frequency stimulation has shown better results in controlling segmental symptoms. However, some studies on the effect of frequency modulation on gait parameters have stated conflicting reports showing better results achieved at low-frequency stimulations (60 Hz).[6-8] Therefore,

we assessed 40 patients for FOG by stimulation at various frequencies—60 Hz, 90 Hz, 130 Hz, and 180 Hz.

Methods

This is an open-label interventional study conducted under the neurology department of a tertiary care hospital (Nizam's Institute of Medical Sciences) in Hyderabad. The study was approved by the Institutional Ethical Committee. Written informed consent was obtained from all the patients. A total of 40 patients with gait difficulties who underwent STN-DBS were included in the study. All the patients were diagnosed with PD by a movement disorder specialist using the United Kingdom Parkinson's Disease Society Brain Bank (UKPDSBB) criteria.[9] They were considered for STN-DBS based on Core Assessment Program for Interventional Therapies in Parkinson's Disease (CAPSIT-PD) protocol.[10] All patients were operated by a qualified neurosurgeon using Leksell frame under MRI guidance with intraoperative 5-channel microelectrode recording. Final lead placement in bilateral subthalamic nuclei was based on the intraoperative stimulation response. Postoperative MRI was performed to confirm the position of electrode after bilateral STN. Monopolar stimulation was performed using the contact within STN as negative and case as positive. All patients were managed on a combination of dopamine replacement therapy as well as DBS.

Best contact

Best contact was selected after assessing the postoperative motor response to individual contact stimulation and based on the location of lead which is identified by the postoperative MRI of the patients. Patients were assessed by a 5-m stand-walk-sit (SWS) test and FOG scoring during medication "ON" state. Since the LEDD (levodopa equivalent dose) was not same in all patients and the OFF periods being short and varied in terms of the severity among patients, the assessments were proposed to be conducted during the ON medication state.

Number of freezing episodes, completion time, and the number of steps were recorded[11]

FOG scoring: This test was performed in a corridor of standardized length 5 meter with an open doorway at the end of it. A 2-meter diameter circle was drawn at the midway of 5 meter distance and the patient was asked to walk straight up to the beginning of the circle, then walk around the circle in clockwise and anticlockwise directions once each, continue for the rest of 5 meters, go through the doorway, and then turn and come back to sit. The same procedure was repeated for two more times once with an object carried in both hands and once with an object and doing a serial substraction of 100-7. The test results—FOG scoring was performed as per the sheet given below [Tables 1 and 2].[11]

Tests were done at four different frequency settings—60 Hz, 90 Hz, 130 Hz, 180 Hz—and device OFF state. There was a 20-min interval before changing the frequencies. In some cases where the assessment took longer duration and the patient went into OFF, reassessment were performed after some time when they entered ON state. To minimize the after effects of high-frequency stimulation, we maintained a gap of 20 minutes. This does not mean inadequacy of low-frequency stimulation. The entire procedure was recorded and a single evaluator used them for calculating the parameters.

Statistical analyses

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

Results

A total of 40 post-DBS patients were studied of which 29 patients were male and 11 were female. The mean age of was 55.45 ± 10.76 years. The mean duration of the disease was 13.12 ± 6.41 years and the mean duration of surgery was 3.58 ± 2.4 years. The mean UPDRS III motor score before DBS in 'OFF' state was 51.5 ± 12.1, and in 'ON' state was 13.3 ± 4.5.

All patients had best response at different frequencies. Mean was calculated for all the parameters recorded. The mean completion time and the mean number of steps taken at the OFF state were 27 and 22 and 20.9 and 20.4 at 180 Hz stimulation, respectively. The mean number of freezing episodes was 1.27 in the OFF state and 0.5 at 180 Hz stimulation. No significant differences were found in terms of completion time, the number of steps taken, and the number of freezing episodes. The mean FOG score in OFF stimulation state was 20.38 and at 180 Hz stimulation it was 9.27. The mean FOG score showed significant improvement at all stimulation frequencies when compared to OFF stimulation. The mean dual tasking score was 8.5 in stimulation OFF state and 5.1 at 180 Hz and was found to be significant.

FOG score and dual tasking improved at all stimulation frequencies when means were compared. Each patient had a maximum response at a particular frequency, which differed for all the patients [Table 3]. We determined a frequency which showed 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, lower number of steps was considered.

Out of 40 patients, 38 patients showed a significant improvement in gait as analyzed with SWS test and FOG score at a single frequency which is different for each patient. In SWS test, 17 patients had good responses at 180Hz frequency, 6 patients had good response at 130Hz, 14 patients at 90Hz, and 5 patients at 60Hz. Two of the patients had best responses at two different frequencies. At 130 HZ, 9 patients had best FOG score and 7 patients had best dual tasking and 6 patients showed best SWS score at this frequency. At 180 Hz, 16 patients had best FOG score and 15 patients had best dual tasking although 17 patients are best at SWS test. At 90 Hz, 13 patients had best FOG score, 12 patients had best dual tasking, and 14 patients had best SWS score at this frequency. At 60 Hz, 5 patients had best FOG score, dual tasking and SWS test [Table 4].

We also compared the gait parameters at best frequency, 130 Hz, and stimulator OFF conditions. The mean completion time at best frequency was 18.50 and at 130 Hz it was 22.33 which was statistically significant ($P < 0.0001$). The mean number of steps was 18.9 at best frequency and 21.48 at 130 Hz ($P < 0.0001$). The number of freezing episodes also were significantly less with best frequency when compared to 130 Hz stimulation (0.28 and 0.65, respectively, $P < 0.0001$). The mean FOG score was 6.45 at best frequency and 9.48 at 130 Hz ($P < 0.0001$). The mean dual tasking score was 3.53 at best frequency and 5.15 at 130 Hz ($P < 0.0002$) [Table 5].

We found relatively higher number of patients responding at 180 Hz (17) and 90 Hz (14) and compared the various clinical parameters [Table 6].

Discussion

Our study showed significant improvement in the gait parameters as assessed by SWS test and FOG scoring which includes dual tasking with a specific frequency of stimulation for each patient. Voltage was kept constant and consequently the total energy delivered changed according to frequency. However, only a change in frequency proved to be beneficial.

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 worsen dynamic postural control, in particular with STN-DBS.[12]

Table 3: Comparison of mean values of various tasks with OFF DBS

Mean±SEM	OFF-DBS	180 Hz	130 Hz	90 Hz	60 Hz
Completion time	27.00±5.64	20.90±2.01	22.28±2.32	21.48±2.45	22.95±2.82
No. of steps	22.73±4.14	20.40±1.03	21.48±1.18	21.03±1.29	22.23±1.84
No. of freezing episodes	1.28±0.43	0.50±0.13	0.63±0.16	0.58±0.16	0.98±0.34
FOG score	20.38±2.05	9.28±1.21#	9.48±1.15#	7.98±1.21#	11.28±1.55#
Dual Tasking	8.56±0.60	5.13±0.63@	5.15±0.58@	4.20±0.57@	5.45±0.59@

Values are mean±S.E.M. (Standard Error of Mean), n=40 in each group; #P<0.05 when FOG score compared to that of OFF-DBS; @P<0.05 when dual tasking compared to that of OFF-DBS DBS=Deep brain stimulation; FOG=Freezing of gait

Table 4: Comparison of frequencies at which patients had best response in SWS test, FOG, and dual tasking

Stimulation frequency	Number of patients with best response on SWS	Percentage	Number of patients with best response on FOG	Percentage	Number of patients with best response on dual tasking	Percentage
130 Hz	6	14.3	9	20.0	7	18.0
180 Hz	17	40.5	16	38.1	15	38.4
90 Hz	14	33.3	13	31.0	12	30.8
60 Hz	5	11.9	5	11.9	5	12.8
Chi square	13.56	8.74	8.51	Chi square	13.56	8.74
P value	0.0035	0.032	0.036	*P* value	0.0035	0.032

SWS=stand-walk-sit; FOG=FOG=freezing of gait

Table 5: Comparison of means of gait parameters at best frequency for individual patient, 130 Hz, OFF state

	Completion time	Number of steps	Number of freezing episodes	Freezing of gait	Dual tasking
BEST	18.50	18.90	0.28	6.45	3.53
130	22.33	21.48	0.65	9.48	5.15
OFF	34.65	29.32	1.65	20.30	8.58
Best vs. 130 Hz*	Z score = −4.9	Z score = −4.7	Z score = −5.21	Z score = −3.86	Z score = −3.77
	P value<0.0001	P value<0.0001	P value<0.0001	P value=0.0001	P value=0.002
Best vs. Off	Z score = −4.7	Z score = −4.9	Z score = −5.2	Z score = −4.3	Z score = −5.01
	P value<0.0001	P value<0.0001	P value<0.0001	P value<0.0001	P value<0.0001

Wilcoxon signed rank sum test was used *Means of gait parameters were compared between best vs. 130 Hz and it was found that the patients responded to best frequency very well compared to 130 Hz for all gait parameters significantly #Means of gait parameters were compared between best vs. Off state and it was found that the patients responded to best frequency very well compared to 130 Hz for all gait parameters significantly

Table 6: Comparison of various clinical parameters of patients best at 180 HZ and 90 HZ

	AGE	DURATION OF DISEASE	UPDRS ON	UPDRS OFF	RT VOLTAGE	LT VOLTAGE
180 Hz	55.7	14.2	12.7	50	2.2	2.3
90 Hz	55.6	13.4	14.9	52.7	2.7	2.85

UPDRS - Unified Parkinson Disease Rating Scale

Few studies have also looked at DBS of the pedunculo-pontine nucleus (PPN) for gait disturbances and have shown that DBS of the substantianigra pars reticulata and PPN have no effect on gait parameters but improves anticipatory postural adjustments and gait postural control.[13,14]

There are very few studies assessing higher frequencies and comparing them with lower frequencies. We attempted to assess the optimal frequency for each patient with regard to gait. Surprisingly, our results do not favor a single common frequency but show that some patients have better response at 180, some at 90, some at 130, and some at 60 Hz. The differences were noted in terms of completion time, number of steps, and lower FOG score which encompasses freezing and festination episodes.

There was a statistically significant difference between stimulation OFF state and the best response frequency, OFF state and 130 Hz. Factors causing the difference could not be determined as there is no significant difference between age, disease duration, pre DBS UPDRS score, and voltage.

A comparison study by Vallabhajosula *et al*. on post STN DBS patients showed that static and dynamic postural control and gait speed significantly improved during 60 Hz and >100 Hz conditions when compared to the OFF condition ($P < 0.05$). There were no significant differences between 60 Hz and >100 Hz stimulation conditions.[15]

Moreau *et al*. (2008) in their study of 13 patients who had undergone STN DBS within 5 years of surgery showed that the number of freezing episodes were 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, voltages ≥3 V led to the greatest improvement in all three parkinsonian signs. The combination of the highest voltage with the narrowest pulse width was most effective.[6]

Valeria Ricchietal (2012) in his study evaluated the effect of 80 Hz stimulation on gait in PD patients who underwent STN DBS and with a follow up of 15 months. 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 3 of 11 patients, the frequency has to be shifted back to 130 Hz after 1 month due to incomplete control of motor symptoms; the rest were continued on 80 Hz up to 15 months. However, gait improvement was no longer detectable by the SWS test at follow-up evaluations at 1, 5, and 15 months.[7]

Our study is only a one-time assessment. But there was no significant change in the UPDRS motor score during the time of examination.

The stimulation frequency of 60 Hz showed significant improvement in swallowing function, FOG and axial symptoms, bradykinesia in post-bilateral STN DBS patients when compared to 130 HZ.[8,16,17]

Hana Brozovaetal (2009) found significant improvement in UPDRS II score (3.9 points; $P < 0.05$) and subscores relating to speech, falling, and walking ($P < 0.05$) when they tried 60 Hz in nine of their post DBS patients who were having speech and gait disturbances on high frequencies. 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.[18]

Our study results suggest that lower frequency STN stimulation may not be the solution to all gait problems in advanced PD. A larger number of our patients benefitted at 180 Hz and 90 Hz stimulation. We also analyzed the effect of frequency change on dual tasking which contributed to most of the FOG score and led to increased gait difficulty of the patient. Best dual tasking score also correlated with best frequency for SWS test in most patients.

This bifurcation confirms that the benefit is definitely due to the frequency change and not just as a result of change in overall energies. 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. In our limited experience, we did not find any distinguishing features between responders at various frequencies. This may be due to small numbers (but largest compared to all the studies done till now up to our knowledge) or other parameters which are not included in this study.

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 did not assess the exact location of the electrode within the STN as that may also probably 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. It is a cross-sectional study and we did not follow the patient for any change in the other measures of PD (as they may be modified by the changes in the energies) and, thus, cannot estimate the overall impact on functional status of the patient.

Conclusion

In spite of the limitations, 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. Both higher and lower frequencies may be beneficial and every PD patient with gait abnormality should be evaluated for best frequency.

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Conflicts of interest

There are no conflicts of interest.

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