Voice Worsening in Post Deep Brain Stimulation Parkinson's Patients - Is Deep Brain Stimulation (DBS-STN) the Culprit?

Commentary

The development of deep brain stimulation (DBS) is attributed to Alim Benabid, who discovered that electrical stimulation of the basal ganglia improved symptoms of Parkinson's disease in the late 1980s.[1] DBS has emerged from its dark and controversial past to become gold standard for advanced and medically refractive Parkinson's disease (PD). The procedure, developed from surgical ablative approaches described in the 1940s, re-emerged in the 1980s in treatment of PD, and the most common targets are subthalamic nucleus (STN) and Globus Pallidus internus (GPi).[1] Deep brain stimulation (DBS) is a neurosurgical procedure, involving implantation of electrodes in specific parts of brain with delivery of constant or intermittent electricity from an implanted battery source.[2,3] The most common indication for DBS is PD, and several trials have shown therapeutic effectiveness of DBS, especially in patients with advanced disease, motor fluctuations, dyskinesias secondary to chronic levodopa, and Refractory tremors. The indications for DBS have expanded to include Dystonia, Obsessive Compulsive disorders, Schizophrenia, Major depression, Bipolar Disorders, and Refractory epilepsy.[2,3] DBS is ineffective for the treatment of axial symptoms (posture, gait, and balance) and may even exacerbate speech, affective and cognitive symptoms. Although STN DBS provides significant improvement in motor symptoms for 5 to 10 years after surgery, the progression of the underlying degenerative process results in deterioration of cognition, gait, and speech problems.[2]

Deep brain stimulation (DBS) of Subthalamic Nucleus (STN) improves limb motor functions consistently, however, DBS shows mixed effects on speech functions. This is due to differential encoding of speech and limb movements in STN neurons. Study by Johari *et al*.,[4] in 12 intraoperative patients and recording 69 single and multi-unit neuronal clusters, higher number of STN neurons were modulated by speech as compared to limb movement, patients with longer disease durations had higher firing rates and there were diverse patterns of modulation in neuronal firing rates in STN for speech and limb movements. Besides, the differential speech and limb movement-related neuronal firing is also explainable by STN functional organization. A Study by Jorge *et al*.[5] have reported improved voice function with DBS-STN at dorsal anterior portion of STN, showing robust speech representation in dorsal STN.

The impairment of speech in PD is related to multiple processes, including prosody, articulation, respiration and resonance. Tanaka *et al*.[6] used Formant frequencies and Vowel Space Area (VSA), which are defined as distinct peaks of acoustic energy produced by individual vowels. In PD patients, dysarthria results from hypokinesia of articulation structures including mouth/jaw and tongue, resulting in smaller articulation working space for vowels. STN-DBS improves hypokinesia of these articulation structures, resulting in improvements in vowel space area (VSA), as compared to medically treated PD patients. However, the improvement in VSA does not co-relate with speech intelligibility in STN-DBS patients during On state. This has been attributed to diffusion of current to surrounding structures, including corticobulbar, cerebellothalamic tracts, medial zona increta, and pre-lemniscal radiations, resulting in dysarthria, respiratory overdrive and abnormal laryngeal muscle contraction.[6]

Wertheimer *et al*.,[7] comparing 287 patients post-DBS and 471 patients without DBS, have shown statistically significant differences in speech disturbance severity in STN-DBS group, independent of age and disease duration. Besides, DBS patients had more significant cognitive deficits, including social interaction and higher Voice Handicap Index (VHI).[7] A cross-sectional study on 76 PD patients treated with bilateral STN-DBS (PD-DBS) and 33 medically treated PD patients, revealed five phenotypes of hypokinetic dysarthria at baseline – relatively good speech and voice, stuttering, breathy voice, strained voice, and spastic dysarthria.[8] DBS-STN significantly ameliorated speech tremors and improved loudness, due to a reduction in hypokinesia, rigidity, and tremor in speech localizing organs. On the other hand, Spastic dysarthria and strained speech were significantly worse in DBS-STB patients during stimulation phase.[8]

The same group, in another report with one year follow-up of 32 patients with DBS STN and 11 medically treated PD patients, reported no statistical significance between the two groups at baseline.[9] However, on follow-up at one year, patients in PD-DBS group had a significantly higher proportion of patients with strained speech and spastic dysarthria as compared to medically treated PD patients, and these phenotypes improved after stopping stimulation. Besides, stuttering and breathy voices were aggravated after DBS-STN, which they attributed this to incomplete glottis closure, asymmetrical glottis movement, and excessive laryngeal muscle contraction in STN-DBS patients.[9]

Tanaka *et al*.[10] in a study of 25 patients (16 patients showing voice and speech deterioration following DBS-STN, and 9 patients remaining stable after surgery), showed that patients with worsening had poorer baseline executive function scores, longer disease duration, poorer UPDRS III Scores, and laterally placed electrodes. In a meta-analysis of 10 articles including 439 patients with PD who underwent bilateral STN-DBS, detailed cognitive evaluation revealed significantly worse

verbal fluency and executive functions than non-surgical group.[11] The declines in verbal fluency scores were associated with decreased perfusion in Pre-frontal cortex, Anterior Cingulate Cortex and Ventral Caudate nucleus on SPECT Imaging. Besides, verbal fluency is also influenced by target location within STN, and studies have revealed that stimulation within ventral associative region is associated with worse verbal fluency performance than dorsolateral sensorimotor area of STN.[11]

The present study featured in this issue is an elegant case–control study which has attempted to specifically address voice impairment in patients post DBS –STN.[12] This study included 66 patients with PD, with 35 patients in STN-DBS group, and 31 patients in Non DBS group. The study has utilized Voice Handicap Index (VHI), Freezing of Gait Questionnaire (FOG-Q) Parkinson's Disease Questionnaire (PDQ-39) and the Schwab and England Activities of Daily Living (ADL) scale to assess FOG, PD-specific health-related quality of life and ADL scale, to assess the patient's ability to function in activities of daily living. This study has not shown significant differences in VHI scores between the two groups, signifying no impact of DBS on speech issues in PD patients. Besides, the VHI and FOG-Q scores correlated consistently with QOL indexes, underlining the clinical significance of Voice impairments in PD.

The STN-DBS group had significantly higher disease durations (*P* 0.006) and Freezing Of Gait Questionnaire scores (*P* 0.008), as compared to non-DBS group, signifying axial impairment in these patients. The axial impairment is DBS unresponsive and worsens with PD duration. Thus, the study concludes that speech impairment in PD patients was a function of the duration of PD, and co-related significantly with axial impairment in PD patients.

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