A Randomized Trial of Deep Brain Stimulation for Parkinson's Disease

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Parkinson's Disease is a chronic and progressive disease. Dozens of medications have entered the marketplace over the last several decades and have helped to alleviate the symptoms of PD. Despite this, however, oral medications remain limited in efficacy due to associated motor fluctuations, which lead to rapid fluctuations between severe akinesia and bothersome dyskinesia. While oral medications are initially very beneficial, they may become less effective over time. Alternatively, at the time of this trial, high frequency continuous electrical stimulation of the STN nucleus, through a surgically-implanted device, had shown benefit for controlling the motor fluctuations in advanced PD. As such, the goal of this study was to compare the efficacy of neurostimulation vs. best medical management alone in advanced PD.

Experimental design and statistics:

Type of study: Randomized controlled pairs trial comparing deep-brain stimulation of the STN nucleus to best medical management alone

Site of study: Multi-center in 10 academic centers across Germany and Austria

Inclusion criteria: Clinical diagnosis of idiopathic PD according to British Parkinson's Disease Society Brain Bank criteria for at least five years prior to enrollment, <75 years of age, and parkinsonian motor symptoms or dyskinesias that limited their ability to perform ADLs.

Exclusion criteria: Dementia or major psychiatric illness and contraindication to surgery

Intervention: This study enrolled patients in pairs, with one patient assigned to neurostimulation within six weeks of enrollment, and then other to best medical treatment. Patients assigned to neurostimulation underwent bilateral stereotactic surgery targeting the STN under local anesthesia. The STN was targeted with MRI, ventriculography, microelectrode recording or a combination of these techniques. The final implementation point was the position at which the most pronounced effect on rigidity and other symptoms of PD was obtained at the lowest intensity during intraoperative testing. The electrode was implanted and confirmed with neuroimaging. The standard pulse setting was 60 microsec/130 Hz and adjusted with voltage to particular patient. Surgical patients were able to continue their PD medications following surgery. Patients assigned to only medical therapy received individualized drug therapy according to guidelines of German Society of Neurology.

Primary outcome:
1) Changes from baseline to 6 months in quality of life assessed by the Parkinson's Disease Questionnaire (PDQ-39)
2) Severity of motor symptoms as assessed by the Unified Parkinson's Disease Rating Scall, Pat-III

Results: 196 patients were screened between 2001 and 2004 with 178 patients meeting criteria. Eligible patients were then divided into pairs with one arm getting surgical DBS and the other getting optimal medical treatment.

a) PDQ-39 Scores: 50 of 78 pairs had improvements from baseline to six months in PDQ-39: Mean PDQ-39 scores were 41.8 (+/- 13.9) at baseline and 31.8 (+/- 16.3) at six months in the neurostimulation group vs. 39.6 (+/- 16) and 40.2 (+/- 14.4) in the medical mgmt. group. This result corresponded to improvement of ~25% in the neurostimulation group compared to medical management. Most significant improvements were obtained for mobility, activities of daily living, emotional well-being, stigma, and bodily comfort. No improvement was seen in terms of in social support, cognition, or communication.
b) UPDRS III Scores: 55 of 78 pairs had improvement in UPDRS-III with improvement in UPDRS-III from 48.0 (+/- 12.3) at baseline to 28.3 (+/- 14.7) at six months in the neurostimulation group. There was no change in the medical mgmt group, with UPDRS-III scores of 46.8 (+/- 12.1) at baseline and 46 (+/- 12.6) at six months. The neurostimulation arm had an improvement of 41% in motor symptoms

Conclusions: This trial was among the first to demonstrate the superior efficacy of neurostimulation over best medical management in advanced PD with levodopa-related motor complications. The results of the study demonstrated significant benefit in both motor fluctuations as well as overall quality of life. Targeting QoL as a primary endpoint was necessary here to show that quality of life is maintained or improved with surgery rather than a mere effect of treatment only on improving motor fluctuations. Further, inclusion of QoL scores here helped to show that neurostimulation and lead placement surgery do not always lead to a decline in cognition, mood, and behavior, as had been suggested in earlier trials. Lastly, cognition and mood have more detrimental effects on QoL than do motor fluctuations, so it was important to ensure a QoL improvement along with motor symptoms in this controlled trial. Otherwise, a limitation to the trial was its lack of blinding and lack of a sham surgery control arm. However, this was not possible as stimulation of the STN would lead to a large decreases in dosage of PD medications, so a blinded comparison with a sham surgery would not be possible. In addition, this trial enrolled only those patients <75yrs old, somewhat limiting it generalizability. Regardless, this study ultimately showed a significant and clinically-meaningful improvement in QoL and UPDRS-III following DBS placement in patients with advanced PD, thus expanding evidence that DBS is a good treatment option for select patients with advanced PD.

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