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Long-term outcomes of deep brain stimulation in severe Parkinson's disease utilizing UPDRS III and modified Hoehn and Yahr as a severity scale

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ABSTRACT

Objectives: Deep brain stimulation (DBS) is the surgical treatment of choice for moderate to severe Parkinson's Disease (PD). However, few studies have assessed its efficacy in severe PD as defined by the modified Hoehn and Yahr scale (HY). This study evaluates long-term and medication outcomes of DBS in severe PD.

Patients and methods: We retrospectively collected the data of 15 patients from 2008 to 2014 with severe PD treated with DBS. Retrospective assessment with the modified Hoehn and Yahr scale and motor subset of the Unified Parkinson's Disease Rating Scale (UPDRS III) were used to objectively track severity and motor function improvement, respectively. Levodopa equivalence daily doses (LEDD), number of anti-PD medications and number of daily medication doses were used to measure improvements in medication burden. Data was evaluated using univariate analyses, one sample paired *t*-test, two sample paired *t*-test, and Wilcoxon signed-rank test.

Results: The mean post-operative follow-up was 44.63 months, average age at diagnosis and the average age at time of DBS was 51.3 years and 61.5 years, respectively, and the time from diagnosis to treatment was 13.2 years. Significant decreases were seen in UPDRS III scores (pre-op = 44.533; post-op = 26.13; p = 0.0094), LEDD (pre-op = 1679.34 mg; post-op = 837.48 mg; p = 0.0049), and number of daily doses (pre-op = 21.266; post-op 12.2; p = 0.0046). No significant decrease was seen in the number of anti-PD medications (pre-op = 3.8; post-op = 3.2; p = 0.16).

Conclusion: Following DBS, severe PD patients demonstrated significant improvements in motor function and medication burden during long-term follow-up. We believe our results prove that DBS is efficacious in the management of severe PD, and that further research should follow to expand DBS criteria to include severe disease.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease, only behind Alzheimer's disease [1]. The incidence varies from 1.5 to 19 per 10,000 people per year, with a steady age-related increase in prevalence [2]. PD is traditionally divided into the phenotypic subtypes of tremor-dominant and akinetic-rigid, based on prominent symptomology [3,4], however the major motor and non-motor components are similar between subtypes [5,6]. The first-line treatment for PD entails medical management with Levodopa, however long-term use is ultimately subject to 'wearing off' symptoms and dyskinesias [7–9]. Deep Brain Stimulation (DBS) is currently the

Abbreviations: DBS, Deep Brain Stimulation; GPi, Globus pallidus internus; HY, Hoehn and Yahr; LEDD, levodopa equivalent daily doses; MoCA, Montreal Cognition Assessment; PD, Parkinson disease; RD, rigid-dominant; STN, subthalamic nucleus; TD, tremor-dominant; UPDRS, III Unified Parkinson Disease Rating Scale III; Vim, ventral intermediate nucleus

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surgical treatment of choice pending declining patient responsiveness to dopamine-based medical therapies, by which high-frequency electrodes are surgically implanted into the brain to improve motor symptomology [10]. Historically, the globus pallidus internus (GPi) and subthalamic nucleus (STN) have been targeted for akinetic-rigid disease [11], while the ventral intermediate nucleus (Vim) is targeted in tremor-dominant disease [12–14].

DBS has proven to safely reduce all of the pathognomonic motor symptoms of PD, and it is therefore the gold standard for surgical intervention, however, it is still considered an adjunct to medical therapy [11]. When combined with medical therapy, DBS accounts for reductions in daily medication doses, in addition to decreased treatment-induced dyskinesia and motor fluctuations [15]. DBS also demonstrates independent motor improvement as assessed by the Unified Parkinson's Disease Rating Scale III (UPDRS III) in short- and long-term studies [10,16–20]. When compared to medical therapy, several studies demonstrate improvements in quality of life, motor function and motor complications with DBS [10,19], however increased behavioral and cognitive complications have been observed, specifically when targeting the STN [21]. As such, the ideal candidates for DBS therapy display mild to moderate medication-related side effects, fluctuating motor symptoms, have few comorbidities and possess no cognitive or behavioral symptoms [22].

Although DBS is established to be an effective treatment for moderate disease burden [23], few studies have been undertaken to assess efficacy in severe disease. This is somewhat counterintuitive, as DBS was pioneered as an effective last resort for the relief of motor symptoms in PD only when alternate medical treatment options had failed [24]. However, the extended application of DBS was quickly realized, and it has since been adapted as an adjunct to medication in the earlier stages of PD. In the literature, the classification of 'severe' disease is used interchangeably with 'late-stage' or 'advanced' disease with a collective definition that is consistent to include intractable and obstructive symptomology with significant functional limitations on lifestyle that display resistance to anti-PD medications [19,25–29]. The reason for the lapse in coverage of this particular subpopulation is most often attributed to a law of diminishing returns, in which severe disease reflects extensive damage to the dopaminergic pathways that may render DBS increasingly less effective and therefore serves as a relative contraindication to surgery [25,27]. This is unfortunate, as PD is one of the most challenging syndromes not only due to its impact on the patient's quality of life, but also on caregiver burden, especially in the presence of severe disease [30].

Recognizing the impact that severe PD has, when left untreated, a small number of studies have undertaken DBS treatment in this cohort with positive overall outcomes [19,26,28,29]. In a 2009 study performed by Weaver et al [19], 121 severe PD patients treated with DBS showed improved motor outcomes, quality of life and neurocognitive function when compared to current medical therapy. Another study of the effects of DBS on severe PD showed increased survival rates following lead placement, and even reduced admission rates to residential care [28]. Still, two more studies have been crucial in enumerating the effects of STN-targeted DBS in these populations [26,29]. However, despite the demonstrated benefits to treating severe PD with DBS, there is still an overwhelming poverty in the literature accounts of treatment in this patient population when compared with mild or moderate disease. This possibly owes to the fact that 'severe disease' is loosely accounted for within the literature with definitions including advanced motor burden, advanced medication burden, increased 'on-time', and even advanced patient age. It is therefore our goal within this study to first define 'severe disease' based on functional disability, and then to use existing measures of PD-associated morbidity to evaluate the long-term outcomes of DBS treatment in a population of patients who carried the diagnosis of 'severe' disease at the time of surgery.

2. Materials and methods

Our study was proposed to and approved by the Institutional Review Board at Ochsner Medical Center (New Orleans, Louisiana, USA). Under the senior author (R.S.), a total of 15 patients were identified to meet our inclusion criteria of having severe PD at the time of DBS lead placement, and their data were retrospectively collected into a password-protected encrypted database. In total 151 patients were treated during the 2008–2014 time frame, and 15 of these were found to have severe PD. Disease severity was described using the modified Hoehn and Yahr (HY) assessment scale to quantify functional disease burden at the time of surgery. Patients with HY stages 4 and 5 were categorized as having severe PD manifestation. Patient-specific data categories that were collected included age at time of diagnosis, age at time of surgery, time between diagnosis and surgery, gender, PD subtype, Montreal Cognition Assessment (MoCA) scores, final DBS electrode target, number of anti-PD medications, and the number of medication doses both pre- and post-operatively. Assessment of medical disease burden was tracked using the levodopa equivalency daily doses (LEDD), number of daily doses, and number of anti-PD drugs as previously discussed. The disease-specific burden on motor symptomology was followed with the Unified Parkinson's Disease Rating Scale III (UPDRS III) both pre- and post-operatively. Statistical evaluation was undertaken using Chi-square to assess demographic data, and paired t-tests and Wilcoxon signed-ranked test to compare the preoperative values of surgical outcomes to the postop and to determine means, standard deviation, standard errors and p-values. Normal distribution testing was not performed. Statistical significance was set at $p < 0.05$.

2.1. Surgical procedure

DBS lead placement for all 15 patients took place at our institution in 3 successive operations pending diagnosis and consent for surgery. An extensive detailing of our surgical procedure and perioperative management is available in a previous publication of our research study series [31]. With the exception of patient-specific electrode targeting, the procedure has remained standardized across our patient population. Within our patient population, 93% of electrode placements were bilateral and performed at either single or staged operations. Only one patient underwent unilateral electrode placement due to symptoms being more pronounced on one side. One patient underwent GPi electrode placement indicated by a rigid-dominant PD, as opposed to STN placement for tremor-dominant disease.

3. Results

From 2008–2014, over the duration of our study, a total of 15 patients were categorized as Hoehn and Yahr stage 4 and 5 at the time of DBS lead placement, which met our study's criteria for 'severe' stage PD. Stages 4 and 5 are defined by loss of independence with daily activities and being wheelchair/bed bound respectively. For these patients, the average post-operative follow-up time was 3.7 years (SD = 1.6 years). Two patients (13.3%) were followed for up to a minimum period of 2 years, 9 patients (60%) were followed for an intermediate period of 2–5 years, and 4 (26.7%) were followed for more than 5 years, which we define as long-term follow-up (Table 1).

3.1. Patient demographics and diagnoses

Of the patients included in our study, 40% were male and 60% were female. The average age at the time of disease diagnosis was 51.3 years old (range = 36–64, median = 54, SD = 9) (Table 1). At the time of surgery, the patients had a range of 0–5 comorbidities (mean = 1.53) (Table 1); with a sub-majority of the patients (33.33%) having 1 comorbidity, where individual comorbidities were not assessed. 13

Table 1
Selected Demographic and Disease Data as well as Treatment Characteristics of HY 4–5 Patients Treated with DBS.

Parameter	N = 15, n (%)	Mean	Median	SD
Sex; female, male	6 (40), 9 (60)			
Age at Dx (range)	36-64	51	54	9
Age at surgery (range)	49-72	61	60	9
Time between Dx and surgery (range)	8-20	13	11	4
Disease sub-classification				
Akinesia-rigid dominant	4 (26.7)			
Tremor dominant	11 (73.3)			
DBS electrodes				
Bilateral	14 (93.3%)			
Single-staged	10 (71.4)			
Multistaged	4 (28.6%)			
Unilateral	1 (6.7)			
DBS target				
STN	14 (93.3%)			
GPi	1 (6.7)			
Number of comorbidities, range	0-5	1.6	1	1.6
No. comorbidities				
0	4 (26.7)			
1	5 (33.3)			
2	3 (20)			
3	1 (6.7)			
4	0 (0)			
5	2 (13.3)			
HY scale				
Preop HY				
Stage 4	13 (86.7)			
Stage 5	2 (13.3)			
Postop HY				
Stage 3	10 (66.7)			
Stage 4	5 (33.3)			
Follow up data in years		3.7	3.5	1.6
< 2	2 (13.3)			
2-5	9 (60)			
> 5	4 (26.7)			

DBS, deep brain stimulation; Dx, diagnosis; HY, modified Hoehn and Yahr; STN, subthalamic nucleus; GPi, globus pallidus interna.

(86.67%) of the 15 patients were categorized as HY Stage 4, while 2 (13.33%) were Stage 5. 73.33% of our patient population was tremor dominant (TD), while 26.67% was rigid dominant (RD). On average, patients carried the diagnosis of PD 13.2 years prior surgery. The average age at the time of DBS surgery was 61 years old (range = 49–72, median = 60, SD = 9) (Table 1). Pre-operative cognition testing with the Montreal Cognition Assessment (MoCA) tool showed that 86.67% of patients had normal scores (≥26/30) and 13.33% of patients had borderline scores (24–25/30).

3.2. Treatment characteristics

DBS in our patient population was most commonly indicated for the presence of 'wearing off' effects of anti-PD medications, and medication-induced motor fluctuations. Within our patient population, the most common target was the STN (93.3%), followed by the GPi (6.7%) with no patients undergoing Vim lead placement. 93.3% of patients underwent bilateral lead placement while 6.7% of patients were treated with unilateral lead placement. Of those who underwent bilateral lead placement, only 28.6% underwent multi-stage bilateral placement with an average of 6 months between lead placements. Bilateral placement was decided upon based on symptom severity. Complications and adverse effects included 2 instances of gait instability and 2 cases of infection, only one of which required replacement of hardware.

3.3. Surgical outcomes

Surgical outcomes in patients with severe PD who were treated with DBS showed positive trends in motor function evidenced by significant improvement from baseline in UPDRS III scores (Fig. 1). Patients experienced a significant reduction of 41% from an average baseline score of 44.53 (SD = 30.19) to 26.13 (SD = 24.9) at post-surgical follow-up (p = 0.009) (Table 2). Patients also experienced a 50% reduction in LEDD (Fig. 2), from a pre-operative average of 1679.34 mg (SD = 886.4) to 837.48 mg (SD = 543.02) after surgery (p = 0.005) (Table 2). This paralleled a 43% reduction in the average number of daily medication doses from an average baseline of 21.26 (SD = 7.6) to 12.2 (SD = 5.36) at post-surgical follow-up (p = 0.005) (Table 2) (Fig. 3). However, the number of anti-PD medications did not significantly change from the pre-operative to the post-operative period. The average number of medications taken by patients at baseline was 3.8 (SD = 0.94), and after surgery it was 3.2 (SD = 1.3), p = 0.06 (Fig. 4). Post-operative MoCA tool assessments remained stable compared to the pre-operative values with 86.7% of patients assessed to have normal cognition and 13.3% assessed to have borderline cognition. MoCA scores remained the same at long-term follow-up when compared to pre-operative values.

4. Discussion

4.1. Background

PD is the second most common neurodegenerative disease affecting the elderly [1], with age-related prevalence rates increasing with the aging population [2]. PD may be further subdivided into RD and TD subtypes based on the primary symptom type [3–6]. The first line of treatment for PD is medical management with Levodopa therapy, however DBS is the surgical treatment of choice pending significant medication side effects [7–11], or failed medical therapy [10,11]. DBS in conjunction with medical therapy accounts for significant decreases in medication burden [15] and motor burden [10,16–20]. Yet, despite proven treatment outcomes, DBS has been recommended to patients with mild to moderate disease, who are refractory to medical therapy [24]. The most commonly cited reason for this apparent neglect in severe PD patient populations is due to extensive cell loss in the substantia nigra that may render DBS increasingly less effective with disease progression [25,27]. It is therefore the purpose of this study to characterize the long-term effects of DBS in the treatment of patients with severe PD.

4.2. Classification and nomenclature

First, we believe that it is necessary to clearly define 'severe PD' as being a functional quantification of the disease. Within the literature, the definitions of severe disease are diffusely heterogeneous to include advanced motor burden, advanced medication burden, increased 'on-time', and even advanced patient age [19,25–29]. In fact, the classification of 'severe' disease is used interchangeably with 'late-stage' or 'advanced' disease with a collective definition that is consistent to include intractable and obstructive symptomology with significant functional limitations on lifestyle that display resistance to anti-PD medications. Advanced disease has been defined elsewhere as worsened bradykinesia, gait instability, speech and swallowing difficulties, and visual hallucinations, with hallucinations usually marking 4 years prior to death; and early PD stages defined by increased rigidity and resting tremor severity [33]. Furthermore, disease severity has also been correlated to cortical and subcortical thinning observed in different brain regions on T1-weighed MRI sequencing [34]. These authors posit that the most accurate surrogate for disease severity is the functional disability caused by the disease, and therefore opted to use the Hoehn and Yahr (HY) scale to stratify our patients. We define 'severe PD' with the description of HY 4 and HY 5 stages, where Stage 4 is characterized by severe disability with the ability to stand and walk without aid, and Stage 5 patients are wheelchair and bedbound without assistance, at the time of DBS lead placement [35].

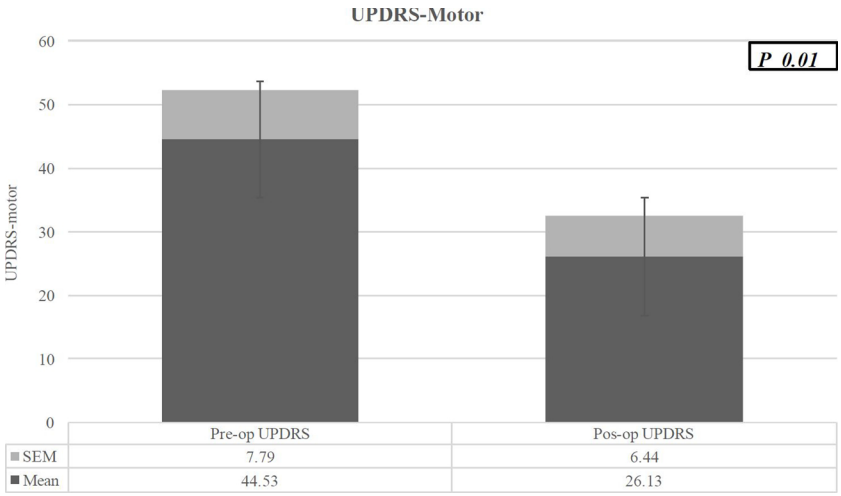

Fig. 1. Direct comparison of preoperative (Pre-op) to postoperative (Post-op) motor score of the Unified Parkinson's Disease Rating Scale (UPDRS-III) showing significance reduction postoperatively. Paired *t*-test and Wilcoxon signed-ranked test were utilized to determine means, standard deviation, standard errors and p-values.

Table 2
Surgical Outcomes in HY 4–5 Patients with Parkinson Disease Treated with Deep Brain Stimulation.

	Preop mean, SEM, SD	Postop mean, SEM, SD	*p-value*
UPDRS-motor	44.53, 7.79, 30.19	26.13, 6.44, 24.9	*0.01*
LEDD	1679.34, 228.86, 886.38	837.48, 140.2, 543.02	*0.005*
No. of Daily Doses	21.26, 1.95, 7.6	12.2, 1.38, 5.36	*0.005*
No. of Daily Medication	3.8, 0.24, 0.94	3.2, 0.32, 1.3	*0.06*
HY scale	4.13, 0.09, 0.35	3.33, 0.1259, 0.49	*0.001*

Pre-op, preoperatively; post-op, postoperatively; UPDRS-III, Unified Parkinson's Disease Rating scale III; LEDD, levodopa equivalency daily dose; No, number; HY, modified Hoehn and Yahr; SEM, stander error of the mean; SD, stander deviation.

4.3. Utilization of DBS for severe PD

Patients with severe PD within our study were treated with DBS as an adjunct to medical therapy. The most common indication for DBS treatment in this population was the development of wearing off symptoms and levodopa-induced dyskinesias that resulted from long-term medical treatment. Following surgical intervention with DBS, a 50% reduction in LEDD and a 43% reduction in daily doses that was maintained with an average follow-up of 3.7 years. When compared to the existing literature, we find that Merola et al [27] showed a 52% decrease in LEDD at 5 years, Lee et al [26] showed a 50% decrease at 6 months, and Deli et al [25] showed a 30% decrease in LEDD at 2 years. The similar levels of success present within these studies further validates our own results and confirms that DBS is effective at controlling medication burden in severe disease which often requires assistance with activities of daily living. Although each study demonstrates varying medication reductions and follow-up durations, all show significant decreases [25–27]. However, it is worth noting that the effectiveness of DBS has shown documented diminution of effect with time [32], which makes direct comparison difficult secondary to differing follow-up periods. Further research will have to be done to extrapolate this phenomenon. Although there is no direct comparison present within the literature for the number of daily medication doses, the significant reduction from 21.27 to 12.2 doses ($p = 0.05$) within our study allows for the avoidance of symptoms associated with long-term levodopa therapy. This results in relief from medication burden, thus improving a patient's quality of life and caregiver burden, especially in the presence of severe disease [23,30].

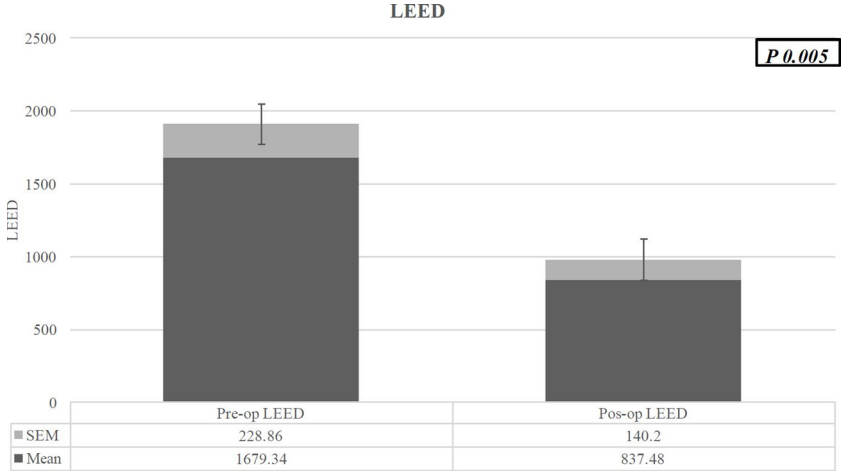

Fig. 2. Direct comparison of preoperative (Pre-op) to postoperative (Post-op) levodopa equivalence daily doses (LEDD) showing significance reduction postoperatively. Paired *t*-test and Wilcoxon signed-ranked test were utilized to determine means, standard deviation, standard errors and p-values.

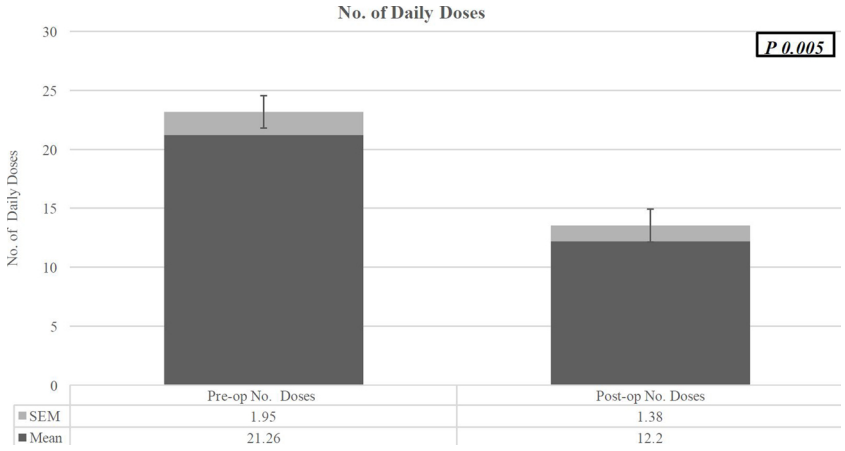

Fig. 3. Direct comparison of preoperative (Pre-op) to postoperative (Post-op) number of daily doses showing significance reduction postoperatively. Paired *t*-test and Wilcoxon signed-ranked test were utilized to determine means, standard deviation, standard errors and p-values.

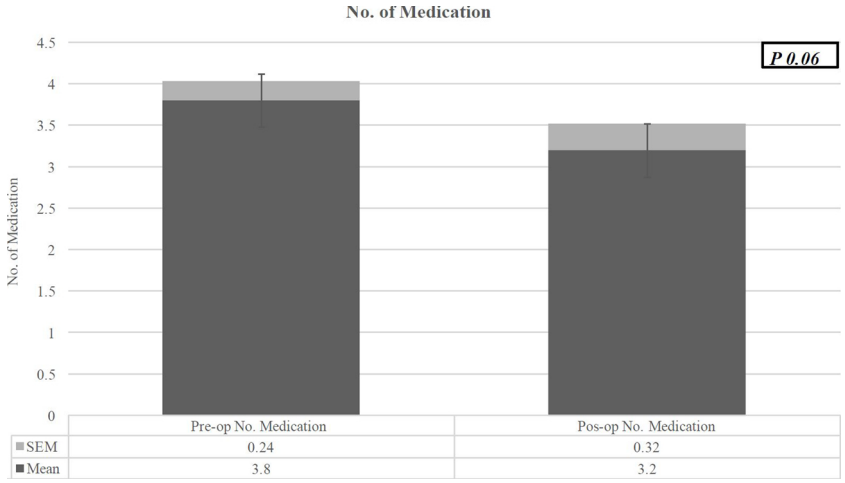

Fig. 4. Direct comparison of preoperative (Pre-op) to postoperative (Post-op) number of daily medications showing trend toward significance reduction postoperatively. Paired *t*-test and Wilcoxon signed-ranked test were utilized to determine means, standard deviation, standard errors and p-values.

4.4. Effects of DBS treatment

Our study is also significant in that it demonstrates improvements in motor function from baseline in patients with severe PD treated with DBS. Reevaluation at 2–5 years showed stable scores thereby indicating that DBS was not associated with increased debilitation. The patients within our study demonstrated a 41% reduction in UPDRS III scores ($p = 0.009$). This improvement is again, consistent with the results present in the existing literature which show 30–45% reductions [26,27,29]. However, the power of our results may be influenced by the lower number of comorbidities present in our population (mean = 1.53) that is unaccounted for in other studies, further attributing to the success in our study's treatment outcomes. An encouraging point within our study was the stability of MoCA scores seen within our patient population at long-term follow-up. Our patients showed no change from baseline values at 3.72 years post-operation, despite commonly-reported declines in cognition within the literature both as a side effect from surgery [21], and as part of the natural disease process [5,6].

4.5. Relevance of length of follow-up

The power and significance of the results present in our study is most profound when taken into account with an average of 3.72-year follow-up in our patient population, with greater than 45% of patients maintaining follow-up between 4–7 years. Although there are several studies that detail significant medication and motor outcomes of DBS in severe disease [19,25–29], only Merola et al [27] possess a longer post-operative follow-up period at 8 years. Their particular study also examined a markedly larger sample size of 203 subjects, which lends credence to the reliability of our comparable results both in medication and motor outcomes. The only other large DBS study to qualify for long term follow up averaged 5–6 years, demonstrating that in 51 patients, the effects of DBS and medication do change in efficacy over time [36]. It should be noted that long-term follow-up involving patients with severe stage disease is logistically difficult, and we therefore believe that our results hold lasting significance in the cannon of studies on DBS in severe PD. It is the well-documented phenomena of diminishing DBS results longitudinally [32] that conveys the importance of long-term follow-up in DBS studies. We further encourage future studies to take the significance of long-term follow-up into account during study planning, and it is our intent to continue to follow our patient population for future supplementation of the literature.

4.6. Comparison with current literature

Overall, the results of DBS treatment demonstrated within our study

suggest that patients with severe PD may benefit greatly from the expansion of inclusion criteria to encompass this population. Our review of the literature has shown that there is little evidence to substantiate exclusion of severe disease from treatment with DBS, as historically, the relative contraindications remain largely speculative. In addition to offering proven decreases in motor and medication burden, a number of studies show strong evidence that both patient quality of life and caregiver burden might be optimized with the use of DBS in this underserved population, so long as the symptomatic benefits outweigh the inherent procedural risks. It is the opinion of these authors that, when aligned with the latter criteria, DBS should be considered a viable treatment option in severe PD.

4.7. Limitations

Our study is not without its limitations. We have presented retrospective data from a single academic center and from a single surgeon with a limited sample size. Additionally, while motor score is often most utilized in Parkinson's research, it neglects the other sequelae of the disease which impact quality of life and disease severity.

5. Conclusion

Our study reports the results of 15 PD patients with severe disease, defined as having Hoehn & Yahr stage 4 and 5 disease at the time of treatment with DBS. Following treatment, patients demonstrated significant decreases in UPDRS III scores, LEDD and the number of daily doses. Our results support the success of DBS in the treatment of both the motor and medication burden of severe PD. Our results are in concordance with the existing literature on the success of DBS as an efficacious treatment modality in severe PD, and are further consistent with overall improvements to the quality of life in both patients and their caregivers in the context of severe PD. Further, our study demonstrates the sustained benefits of DBS in this population with an average post-operative follow-up period of 3.72 years. The success of DBS present within our study suggests that the presence of severe disease should no longer be considered a strong contraindication to treatment with DBS. It is the hope of these authors that our study might act to inform future treatment considerations in severe PD and encourage future research within this subpopulation.

Disclosure

The authors have no financial or proprietary interest in the subject matter of this article.

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