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Deep brain stimulation of the subthalamic nucleus in Parkinson's disease patients over 75 years of age

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ABSTRACT

Introduction: Deep brain stimulation (DBS) is an effective therapy for Parkinson's disease (PD). However, its effect in older patients is not extensively studied, as they are often excluded from DBS surgery due to concerns of complications or reduced benefit. We assessed clinical outcomes after subthalamic nucleus (STN) DBS in older patients (age > 75 years) with PD.

Methods: All PD patients above 75 years who underwent STN-DBS between 1999 and 2015 were included. Unified Parkinson's Disease Rating Scale (UPDRS) scores and Parkinson's Disease Questionnaire (PDQ-39) scores were assessed up to 4 years after surgery. Other measures included were complications/adverse events, levodopa equivalent dose, and cognitive function.

Results: A total of 30 patients underwent 52 lead placements. Mean age at surgery was 77.5 years (range 75.0–84.5 years). Post-DBS, motor scores improved by 30.8% after 1-year and 27.3% after a mean of 2.5 years ($p < .001$). All motor sub-scores improved, however axial signs did not change over time. OFF time and dyskinesia duration reduced significantly ($p < .001$), whereas quality of life, activities of daily living and cognitive function did not significantly change. The following adverse events were noted: transient post-operative confusion (36% of patients), gait difficulty (13.3% of patients), hemorrhage (3.8% of leads), personality changes (3.3% of patients), lead revision (1.9% of leads), seizure (1.9% of leads), and infection (1.9% of leads).

Conclusions: STN-DBS improves motor outcomes in patients over 75 years of age; however, there was no change in quality of life. Although post-surgical transient confusion was common, there were no serious adverse events and the incidence of other complications was typical for DBS surgery.

1. Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective treatment option for patients with Parkinson's disease (PD) [1–5]. The therapy is indicated for patients with advanced motor symptoms and complications which are not consistently controlled with medications. With the results of the EARLYSTIM trial, the therapeutic window has been expanded to include PD patients with early development of motor fluctuations and dyskinesia [6]. However, the age for DBS candidacy is not clearly defined and older patients are often excluded due to concern for complications and/or reduced benefit. A few studies have examined the effect of DBS in older PD patients and have shown improvement in motor scores and dyskinesia in a small number of patients [7,8]. Over the next few decades, as life expectancy is rising [9], the prevalence of PD in the older population is predicted to increase [10]. Thus it is likely that more older patients will be referred for surgical therapy options namely DBS. The literature on clinical outcomes in patients above 75 years of age is limited. Therefore, efficacy and safety data for DBS in this age group are important to guide clinicians in selecting the appropriate therapy. We report clinical outcomes of patients at least 75 years of age who underwent STN-DBS.

2. Methods

We reviewed prospectively collected DBS data to identify patients of at least 75 years of age with a diagnosis of idiopathic PD who underwent STN DBS surgery at the University of Kansas Medical Center from 1999 to 2015. Determination for DBS surgery was done by a multidisciplinary team based on patients' clinical characteristics, response to prior treatment and quality of life. All the patients underwent neuropsychology testing, with a Dementia Rating Scale (DRS-2) [11] score > 120 prior to DBS surgery. Patients underwent DBS lead

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placement bilaterally or unilaterally using microelectrode recording (MER) guidance. Surgery was performed by two neurosurgeons. Assessments were performed preoperatively, 6-months postoperatively, and annually thereafter.

The change in motor function and ADLs after STN-DBS was assessed with the Unified Parkinson's Disease Rating Scale (UPDRS Part II and III) [12] and quality of life (QoL) with the Parkinson's Disease Questionnaire (PDQ-39) [13], up to 4 years after surgery. Changes in individual cardinal signs were assessed separately by adding sub-scores from the UPDRS part III scale: tremor (items 20, 21), rigidity (item 22), bradykinesia (items 23,24,25,26 & 31) and axial (items 27, 28, 29, 30). Dyskinesia and OFF time were assessed using UPDRS part IV, items 32 (duration of dyskinesia) and item 39 (proportion of the day in "off" state), respectively (scale 0–4 with 0 = none, 4 = 76%–100% of waking day). Other measures included were complications/adverse events, levodopa equivalent daily dose (LEDD) [14], Mini Mental State Examination (MMSE) [15], Epworth Sleepiness Scale (ESS) [16] and patient global impression (PGI). In 2007, our institution practice changed from using MMSE to Montreal Cognitive Assessment (MoCA) [17] for assessing cognitive function. For the data analysis we used a standardized algorithm to convert MoCA scores to MMSE [18]. Pre- and post-DBS scores were compared after a mean follow-up of 1 year and 2.5 years (range 1.9 to 4.3 yrs). Pre-surgical ON and OFF scores were compared with paired *t*-tests. Analysis of variance was used to examine changes in all measures across visits with Bonferroni post-hoc comparisons. Unilateral and bilateral patients were analyzed separately; however, majority of the data is presented for the entire cohort as there were no differences between the groups. Significance was set at $p < .05$.

3. Results

3.1. Patient baseline characteristics

Thirty PD patients who underwent STN-DBS after the age of 75 years were identified. A total of 52 leads were implanted, of these 22 were implanted bilaterally and 8 were implanted unilaterally. The mean age of patients (male 21 and female 9) at the time of surgery was 77.5 ± 2.1 years and the mean duration of disease was 11.8 ± 5.3 years. Pre-DBS, the mean percentage improvement in UPDRS part III motor score on levodopa was 37.4%. Improvement was seen in all the subscores: tremor (69%), bradykinesia (35.8%), rigidity (37.2%) and axial (40.3%). The baseline clinical characteristics of the patients are summarized in the Table 1.

3.2. UPDRS motor and activities of daily living (ADL) scores

Across all patients included in the analysis post-DBS UPDRS part III total score OFF medication/ON stimulation improved significantly when compared to pre-DBS OFF medication baseline scores (Table 1). The mean UPDRS III scores improved from 42.8 ± 7.1 to 29.6 ± 7.7 after a mean follow-up of 1 year (n = 27), and to 31.1 ± 5.9 after a mean follow-up of 2.5 years (n = 16), which corresponds to an improvement of 30.8% at 1 year and 27.3% at 2.5 years ($p < .001$). Significant improvement was seen in the tremor, bradykinesia and rigidity motor sub-scores ($p < .001$); however, the axial motor subscores did not change significantly over time ($p = .40$). There was also a significant improvement in UPDRS part IV, dyskinesia duration and OFF time ($p < .0001$).

Motor outcomes were also examined separately for patients with unilateral and bilateral DBS. In the bilateral DBS group (n = 22), UPDRS III scores improved from 42.9 ± 6.0 to 30.6 ± 6.6 after a mean follow-up of 1 year (n = 20) and 31.7 ± 5.7 at 2.5 year (n = 14), which corresponds to an improvement of 28.6% and 26.1% respectively ($p < .001$). There was also significant improvement in dyskinesia duration and OFF time ($p < .001$). Patients who had unilateral STN DBS (n = 9) also had a significant improvement in motor scores from 42.7 ± 9.9 to 26.8 ± 10.3 after a mean of 1 year and 27.0 ± 8.4 after a mean of 2.5 years, corresponding to 37.2% and 36.8% respectively ($p = .019$). There was no significant improvement in dyskinesia duration or OFF time with unilateral DBS. There was an improvement in UPDRS part II ADL scores after STN DBS for the group as a whole; however, improvement was not statistically significant. No significant changes in ADL scores were seen in bilateral or unilateral groups.

3.3. Quality of life

For the overall group, QoL did not improve significantly after STN DBS (Table 1). There was a slight improvement in PDQ-39 total scores after 1 year but these worsened after a mean of 2.5 years ($p = .33$). Similarly, no significant change in PDQ-39 total score was seen when analyzing bilateral and unilateral DBS groups separately. In the bilateral DBS group; however, PDQ Bodily discomfort scores improved significantly over time ($p < .03$).

3.4. Cognitive measures

We used MMSE, PDQ-39 cognition sub-scores and UPDRS part I mentation scores to assess changes in cognition after STN DBS. In the

Table 1
Baseline and post-surgical outcomes.

Measures mean (SD)	Pre-DBS scores			Post-DBS scores		
				1 year	2.5 year	
UPDRS scores	OFF meds	ON meds	p	OFF meds/ON Stim	OFF meds/ON stim	p
	(n = 30)	(n = 29)				
Mentation	2.2 (1.8)	–	–	2.6 (1.8), n = 28	3.7 (2.4), n = 20	0.027
ADL	19.2 (5.8)	12.5 (4.7)	< 0.001	16.6(6.5), n = 28	18.7(6.5), n = 20	0.240
Total	42.8 (7.0)	26.8 (6.2)	< 0.001	29.6 (7.7), n = 27	31.1(5.9), n = 16	< 0.001
Motor	5.0 (4.5)	1.5 (2.4)	< 0.001	0.66 (1.4), n = 27	0.31(0.6), n = 16	< 0.001
Tremor	10.2 (2.6)	6.4 (2.7)	< 0.001	6.7 (2.9), n = 27	6.2 (2.2), n = 16	< 0.001
Rigidity	15.4 (3.0)	10.0 (2.2)	< 0.001	11.4 (3.4), n = 27	12.4 (3.0), n = 16	< 0.001
Bradykinesia Axial	7.8 (3.4)	4.8 (2.2)	< 0.001	6.7 (3.1), n = 27	7.7 (2.4), n = 16	0.402
Total PDQ-39		34.9 (13.9)		32.1(12.8), n = 26	38.7 (17.4), n = 20	0.326
UPDRS IV, Dyskinesia duration		1.0 (0.8)		0.14 (0.3), n = 28	0.15 (0.6), n = 20	< 0.001
UPDRS IV, OFF time		1.1(0.7)		0.29 (0.5), n = 28	0.4 (0.8), n = 20	< 0.001
LEDD mg		1318.9 (655.8)		688.6 (451.8), n = 28	602.5 (302.7), n = 20	< 0.001
ESS		10.8 (5.3)		9.0 (4.5), n = 22	10.95 (5.7) n = 19	0.424
MMSE		28.1 (2.9)		26.77 (3.6), n = 26	25.8 (3.2), n = 19	0.065

overall group, MMSE scores slightly worsened after STN DBS; however, the change was not statistically significant ($p > .05$). Similarly, no significant change was seen in PDQ-39 cognition sub-scores. However, UPDRS part I mentation scores worsened in the overall group ($p < .03$) and in patients who had bilateral DBS ($p < .01$), but no significant change was seen with unilateral DBS.

3.5. Levodopa equivalent daily dose, epworth sleepiness scale and global impression scores

The mean levodopa equivalent daily dose (LEDD) was reduced from 1318.9 mg before surgery to 688.6 mg after a mean follow-up of 1 year and 602.5 mg after a mean follow-up of 2.5 years in the overall group. This represents a reduction of 47.8% at 1 year and 54.3% after a mean of 2.5 years ($p < .001$). A significant reduction was seen after bilateral STN DBS, whereas in the unilateral STN group, LEDD reduction was not significant.

No significant changes in ESS scores were seen after surgery.

Based on patient global impression scores for which data was available, in the overall group, at 1 year ($n = 27$) 66.6% patients reported marked, 22.2% reported moderate and 7.4% reported mild improvement. After a mean of 2.5 years ($n = 18$), 88.3% reported marked, 5.5% ($n = 1$) reported moderate, 5.5% reported mild improvement. One patient reported mild worsening.

3.6. Adverse events

The most common surgical adverse event was post-operative transient confusion in 11 patients (36%), followed by hemorrhage in 1 patient and seizure in 1 patient (1.9% of leads). Other complications included worsening of gait and balance in 4 patients (13.3% of patients) and personality changes in 1 patient (3.3% of patients). There was one patient who had infection requiring replacement of one lead (1.9% of leads) and 1 patient underwent revision surgery due to poor benefit (1.9% of leads). In 3 patients, the surgical procedure had to be aborted due to fatigue, poor test stimulation and poor trajectory. Of these, 2 patients had surgery done later and 1 remained with unilateral DBS.

4. Discussion

In the present cohort, STN-DBS in patients above 75 years of age resulted in a significant improvement in motor scores, OFF time and dyskinesia duration up to 4 years after DBS placement. In addition, the LEDD was reduced by around 50%. Improvement in motor scores were comparable to previous reports of improvement between 25 and 46% [1–5]. It is important to note that the mean age of patients included in these studies was around 60 years at the time of DBS surgery [1–5]. Studies comparing the effect of DBS in patients above and below 65 years of age have found no significant difference in improvement in motor scores, dyskinesia or OFF time [19,20]. However, there is very limited literature on clinical outcomes after STN-DBS in patients above 70 years of age. Russman and colleagues studied 52 PD patients with a follow-up of 6 to 48 months after STN-DBS and compared outcomes between older and younger patients. There were 13 patients above 70 years of age (mean age 74 years), 24 patients between 60 and 70 years and 15 patients were below 60 years of age. They found no significant difference in improvement in motor scores and dyskinesia between the groups. In the older group (> 70 yrs), post-DBS, motor scores OFF medication improved by around 22%, however ON medication scores and axial scores worsened over time [8]. Another study reported 51% improvement in motor scores in patients above 70 years of age ($n = 37$, mean age 72.4 years) after a mean follow up of 42 months (range 4–84 months) post-operatively [21]. In another study, the effect of age and disease duration on rigidity and dyskinesia scores after DBS was assessed. At 1 year, patients above 70 yrs. ($n = 10$, mean age 73.9 yrs) had a significant improvement in dyskinesia scores, but rigidity did not change significantly [7].

In our study, older patients had significant improvement in motor scores (27.3%) at mean duration of 2.5 years, representing improvements in tremor (93.8%), rigidity (38.7%) and bradykinesia (19.3%), which were sustained up to 4 years. Interestingly, the axial sub-score which responded well to levodopa prior to surgery did not change post-surgery. It is unclear whether lack of improvement in axial signs is due to limited response of stimulation on axial scores versus the contribution of factors such as disease progression, reduction in levodopa and worsening of concomitant musculoskeletal issues. We also noted that improvement in bradykinesia scores reduced over time, this is likely due to decrease in therapy response with disease progression and contribution of age-related comorbidities on motor symptoms. The mean age of patients in our study was 77.5 years which was higher than the previously reported studies. Our findings together with the results of previous studies suggest that patient age at the time of DBS surgery is not a strong predictive factor for motor outcomes after DBS.

There are very limited data on QoL after DBS in older patients. We found no change in QoL over time and our results were similar to a prior study, in which no improvement in quality of life was seen in patients above 70 years of age who underwent STN-DBS [20]. Although we noted improvement in ADL scores compared to pre-DBS baseline, the difference was not significant. On the contrary, Russman and colleagues reported worsening of ADL scores in older patients (> 70 yrs) by around 40% after STN-DBS [8]. There was no significant improvement in QoL in our cohort as compared to good improvement in QoL in younger patients [5,6]. We believe that different factors can account for these findings, including multiple concomitant comorbidities in an older population such as arthritis, hip and knee replacement, degenerative disc disease of spine, lack of improvement in axial symptoms and worsening of non-motor symptoms, all of which can impact quality of life [22]. Further studies are needed to look at impact of different factors including multiple concomitant comorbidities in this age group on ADLs and QoL. The reduction in levodopa therapy after STN-DBS may also contribute to worsening of non-motor symptoms.

Most of the studies done in older patients have not examined the effect of STN-DBS on cognition. We assessed cognitive function using MMSE, PDQ-39 cognition sub-scores and UPDRS Mentation scores. We found no significant changes in cognition after DBS surgery using these measures. Although a detailed neuropsychological assessment is more sensitive for cognitive impairment in PD [23], the majority of our patients did not have neuropsychological testing after DBS surgery, thus limiting our assessment of cognitive changes. Our findings may have under-estimated the degree of cognitive changes after DBS in the older age group and future studies are needed to look at the neuropsychological profile in older persons after DBS. However, our results are similar to a previous study in which post STN-DBS no significant cognitive changes were noted in patients above or below 65 years of age [20]. We noticed worsening of UPDRS part I mentation scores and a post-hoc analyses revealed that this worsening was mostly due to increased apathy and depression.

Overall, the complication rate was similar to that reported in younger patients [24], except for a relatively higher incidence of transient post-operative confusion which was not surprising for this age group. Other studies comparing effects of STN-DBS between older and younger patients found no difference in complication rate [7,8,19,20]. In a large retrospective analysis, Delong et al. studied the effect of increasing age on short-term complications after DBS surgery. In their study, patients of age 75 years or older ($n = 123$) were found to have a similar complication rate within 90 days of DBS surgery compared to younger patients [25]. However, this study did not report motor outcomes in different age groups and complications with respect to different DBS targets were not analyzed.

Although the current report presents clinical outcomes after STN-DBS in the largest cohort to date of patients at least 75 years of age at the time of surgery, there are limitations to this study. Motor scores

were collected in an open-label fashion increasing the risk for overestimation of clinical improvement. Also, we had a 30% reduction in sample size at the mean follow up of 2.5 years subjecting this study to attrition bias; however, attrition in a cohort of older adults is common. There were a total of 30 patients over 75 that received DBS; 28 that had a 1-year visit (2 did not return for 2 years) and 20 that had a second follow-up visit. The 10 patients not included in the longer follow-up are missing for various reasons: 5 had not reached the 2-year follow-up at the time of data analysis; 3 moved out of state and were no longer seen at the site; 1 was lost to follow-up and later died 11 years after DBS; and 1 died prior to the 2-year visit. As the clinical outcomes are from a single center, pooling data in this age group across different centers will help in generalization of these findings. Despite the limitations of this study, our results suggest that age should not be a strong consideration in selecting patients for DBS. Future prospective studies, across different centers are needed to further guide clinicians regarding DBS candidacy in older adults.

Declarations of interest

None.

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