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Long-term Results for Single Channel-Guided Deep Brain Stimulation Used to Treat Parkinson's Disease

Parkinson Hastalığının Tedavisinde Kullanılan Tek Kanallı Derin Beyin Stimulasyonun Uzun Süreli Sonuçları

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ABSTRACT

Introduction: The optimal method for targeting the subthalamic nucleus (STN) and positioning the deep brain stimulation (DBS) electrode is still controversial. In this study, single channel-guided stimulations were used in order to determine the most proper way to target the STN. Findings were synthesised for use in clinical situations. This paper presents the long-term results of DBS applied using single-channel guidance.

Methods: We retrospectively reviewed 15 patients who had undergone STN-DBS to treat Parkinson's disease in-between 2010 and 2017. All patients were examined preoperatively, and they were routinely followed-up 2–7 years postoperatively.

Results: The use of single-channel guidance resulted in better outcomes of motor complaints of Parkinson's patients. Moreover, a significantly greater improvement in Unified Parkinson's Disease Rating Scale Score (UPDRS) was achieved in either ON or OFF periods of patients.

Conclusion: Single channel-guided STN-DBS is a safe procedure and it results in improved motor outcomes in advanced Parkinson's Disease.

Keywords: Deep brain stimulation, microelectrode recording, Parkinson's Disease, subthalamic nucleus

ÖZ

Amaç: Subtalamik çekirdeğin (STN) hedeflenmesi ve derin beyin uyarımı (DBS) elektrodun konumlandırılması için en uygun yöntem hâlâ tartışılmaktadır. Bu çalışmada, STN'yi hedeflemenin en uygun yolunu belirlemek için tek kanallı stimülasyonlar kullanılmıştır. Bulgular klinik kullanım için sentezlenmiştir. Bu çalışmada tek kanal kullanılarak uygulanan DBS'nin uzun dönem sonuçları sunulmuştur.

Yöntem: 2010 ile 2017 yılları arasında Parkinson hastalığını tedavi etmek için STN-DBS uygulanan 15 hastanın geriye dönük olarak incelenmiştir. Hastalar preoperatif olarak incelenmiştir. Ameliyattan 2–7 yıl sonra rutin takipleri yapılmıştır.

Bulgular: Tek kanal STN-DBS kullanılması ile iyi motor sonuçları ortaya çıkabilmektedir. Ayrıca, Birleşik Parkinson Hastalığı derecelendirme Ölçeği Skoru (UPDRS) değerinde hem ON hem de OFF döneminde daha yüksek iyileşme elde edilmiştir.

Sonuç: Tek elektrod ile uygulanan STN-DBS diğer metodlarla da kombine edildiğinde güvenli bir işlem olarak ortaya çıkmaktadır.

Anahtar Kelimeler: Derin beyin uyarımı, mikroelektrot kaydı, Parkinson hastalığı, subtalamik çekirdek

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INTRODUCTION

Not only the Parkinson's Disease (PD) but also the other areas of medicine are found in the place of DBS treatment; these areas are in numerous central nervous system disorders including intractable epilepsy, chronic pain, cluster headache, and mainly some psychiatric disorders such as treatment-resistant depression, bipolar disorder, anorexia nervosa, obsessive compulsive disorder, Tourette's Syndrome, the other condition such as drug addiction, obesity and most recently Dementia, especially Alzheimer's disease.

Subthalmic nucleus (STN) deep drain stimulation (DBS) is an effective treatment for advanced Parkinson's disease (aPD). However, the success of this surgery depends on the accuracy of the target. STN-DBS is being investigated and applied to treat cardinal symptoms of PD, as well as motor fluctuations and dyskinesia. Direct and indirect methods are used to reach the intended target. Recording with multiple implanted electrodes can increase the risk of bleeding.

In particular, young patients ranging in age from 50's to their early 60's, with cardinal symptoms that principally respond well to levodopa (L-dopa), can be effectively treated using STN-DBS. STNs are tiny, unique structures and their location in the brain is typically calculated preoperatively with magnetic resonance imaging (MRI). Different surgical

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techniques have been used. Target selection and trajectory planning are often done automatically or manually via magnetic resonance (MR) and computed tomography (CT) (MR-CT) fusion. However, the best way to obtain the result is still being discussed. Different surgical approaches are used in different medical centres. In this study, we tried to synthesise these methods by considering their ability to target the STN. This paper reports on the long-term results of the STN-DBS approach applied using single-electrode guidance (1–12).

METHODS

We retrospectively reviewed 15 patients who had undergone STN-DBS to treat PD between 2010 and 2017. Good L-dopa response was an inclusion criterion. Exclusion criteria were marked atrophy or other focal brain abnormalities based on MRI results.

Hoehn and Yahr Staging of PD and the Unified Parkinson's Disease Rating Scale (UPDRS) (preoperative-postoperative), Florida Surgical Questionnaire for Parkinson's Disease (FLASQ-PD) and Mini-Mental State Examination (MMSE) were used. We did not administer DBS to patients that did not pass the mini-mental test or that had severe psychiatric disease. The study was approved by the Ethics Committee of Selçuk University Medical School (20.12.2017-22). There are patient approval.

Surgery

Patients were evaluated by a multidisciplinary team of neurosurgeons, neurologists and psychiatrists and then underwent surgery for implantation of STN-DBS. Anti-Parkinson drugs (APD) were arranged in 24 hours before surgery. The patient was fitted with a stereotactic frame using local anaesthesia. Brain CT and MRI were used to identify the coordinates of the targets. The target was defined from fused images. MRI (T1-weighted Gd-enhanced, T2W unenhanced) data were used to avoid puncturing the vascular structures and the lateral ventricles. Direct methods (MRI images with definition) and in direct methods (stereotactic, anatomical landmarks, microelectrode recording [MER] and macro-stimulation) were used to reach the right target precisely. The STN was identified as a hypo-intense almond-shaped structure as seen in the MRI. Additionally, a red nucleus (RN)-based target could be defined from the MRI. We were able to reach the STN with reference to the RN. The indirect method could be applied using MRI to identify the anterior commissure (AC) and posterior commissure (PC) with standard human brain atlases.

We manually calculated the x, y and z coordinates and AC-PC to detect the target. A burr hole was made in the frontal portion of the skull. Single-track MER and macro-stimulation were carried out to confirm the effect of stimulation. The responses were evaluated by neurologists and neurophysiologists. We used all the methods available to determine the target and identify where to place the final electrode. After synthesising all these methods, we obtained the desired result with a single MER. Based on the clinical situation localisation was detected as a result of this synthesis. We placed the final electrode.

X-rays were also used to identify the actual position of the electrode. The condition was repeatedly checked with postoperative brain mapping and CT.

Following implantation of the STN-DBS, a generator was placed in a subcutaneous pocket of the infra-clavicular region while the patient was under general anaesthesia. Three days after surgery, the patient was discharged from the hospital and the battery was activated around 15th days after surgery.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS 11.0 for Windows Version; Chicago, IL, USA) packaged software was used for data analysis. Descriptive statistics (mean, median) and nonparametric analysis were used as statistical analyses. Wilcoxon signed-rank test was used for pre-postoperative comparison of the quantitative data. Statistical significance level was established at P=0.05. The final preoperative and postoperative control values were analysed.

RESULTS

We retrospectively reviewed 15 patients who had undergone implantation of STN-DBS electrodes to treat PD. We performed follow-up of all patients for a period ranging from 2 to 7 years. Of the 15 patients, 11 (73.3%) were women and 4 (26.7%) were men. The median age of the patients at the time of surgery was 63 (58±6.18 years [52–71]). PD duration was 11.3±3.47 years; and the disease had been advanced stage in these patients for the past 4.6±1.50 years. The most obvious complaints were prolonged and common ON-OFF period with or without tremor (86.7%), dyskinesia (6.7%) and gait disturbance (6.7%). The length of surgery with targeting was 7.26±0.77 hours (6–8.5) hours. The preoperative Hoehn and Yahr stage score was 3.7±0.59. The Florida Surgical Questionnaire score was 31.7±2.59 (Table 1). The mean improvement of patients with a UPDRS was compared before and after surgery when they were ON and OFF period. The preoperative results were 60.5±16.9 and 71.5±18.5. The postoperative results were 34.0±10.1 and 54.2±18.2, respectively. This represents a decreased rate of UPDRS 56% and 75% for the preoperative and postoperative results, respectively.

A statistical difference was found between the preoperative ON period and postoperative ON period results and between the preoperative OFF period and postoperative OFF period results (P=0.001) (Table 2).

The mean stimulation programming results for the first control and last control (left STN) channels were 124.9±49.4 Hz (90–240 Hz), 128.5±2 Hz (60–240 Hz); 2.2±1.1 V (1–4 V) and 2.15±1.5 V (1.5–4.0 V); 69.0±23.7 microseconds (µs) (60–90 µs) and 68.7±3.9 µs (60–91 µs), respectively. A statistical difference was found between the stimulation amplitudes (P=0.011) (Table 3).

The mean stimulation results for the first control and last control (right STN) were 115.2±56.5 Hz (90–240 Hz), 113.9±60.6 Hz (60–240 Hz); 1.8±1.03 V (1.0–3.4 V) and 2.58±1.37 V (1.5–4.5 V); 57±25.3 µs (60–90 µs) and 6.73±27.9 µs (60–91µs), respectively. A statistical difference was found between the stimulation amplitudes (P=0.010) (Table 3).

Table 1. Baseline characteristics

Characteristic	n	
Sex		
Male	11 (73.3%)	
Female	4 (26.7%)	
Age		
Mean ± standard deviation	63.4±6.18	
Range	52–71	
PD Duration (Total-increase)		
Mean ± standard deviation	11.3±3.47	4.6±1.50
Range	7–19	3–8
Surgery time		
Mean ± standard deviation	7.26±0.77	
Range	6–8.5	
Hoehn and Yahr stage		
Mean ± standard deviation	3.7±0.59	
Range	2–4	
Florida Surgical Questionnaire for Parkinson Disease		
Mean ± standard deviation	3.7±0.59	
Range	27–35	

Table 2. Changes in Unified Parkinson Disease Rating Scale scores Pre-Postoperatively medication-on/off phase

Score	Preop. ON*	Preop. OFF*	Postop. ON*	Postop. OFF*
UPDRS				
Mean ± standard deviation	60.5±16.9	71.5±18.5	34.0±10.1	54.2±18.2
Range	32–89	41–100	20–56	30–72
P Value	<0.01	<0.01		

* Preoperatively medication-on/off phase, Postoperatively (Last Control) medication-on/off phase.

STN stimulation resulted in a profound significant decrease in the L-dopa equivalent dose between the first and last control: 873±175.4 mg and 434.8±127.6 mg respectively. A statistical difference was found between these values (P=0.01) (Table 3), and the dosage rate decreased by 49%. The stimulation polarity, unipolar/bipolar rate ranged from 26.7% to 66.7%. The majority of patients received monopolar stimulation. During the follow-up period; the stimulation rate of 11 patients changed, but our contact points did not change; our first and last contract point was the same with 73.3%.

In terms of complications, one patient developed a local infection around the extension cable, which was successfully treated with antibiotic therapy. One patient developed aggressive behaviour, but recovered after a short time. In another patient, the postoperative CT scan showed pneumocephalus and small haemorrhages, but the clinical effect was not seen.

DISCUSSION

This paper presents a synthesis of all available techniques that can be used to correctly target the STN with single-electrode guidance. Since the first description of DBS leads to the use of an implantation technique in the STN (1993), STN-DBS can be applied effectively and safely using various approaches. The STN could be functionally divided into three parts, including an antero-dorso-laterally-located motor part, a ventro-medially-located associative part and a medially-located limbic part. The antero-dorso-lateral motor part is used to obtain the best possible results for motor symptoms and decrease the risk of behavioral complications (13, 14).

The optimal method for targeting the STN and positioning the DBS electrode is still being debated. Some studies have advocated direct targeting using MRI, but others have found that electrophysiological mapping is useful for refining the precision of the procedure (15–19).

Due to the close anatomic relationship between the RN and the STN, the borders of the RN could be used as an internal reference. The RN can be easily located on T2-MRI.

Optimal preoperative radiological targeting of the STN may decrease the number of trajectories necessary to find the optimal location for stimulation, thereby decreasing the time and morbidity associated with the procedure. Thus, we used electrophysiology to ascertain the final electrode position.

MRI or MR-CT fusion studies were performed postoperatively to determine the accuracy of STN localization. One of the drawbacks of using MRI is that artefacts, distortion, heating and functional disruption may arise. In MR-CT fusion, there might be a problem achieving the correct result with shifts in brain. Thus, MR-CT would be a very good approach to determine target accuracy during surgery.

In the present study, all appropriate methods were used in order to target the STN in the most accurate way, then the results were analyzed and synthesized to determine the best approach to use in a clinical situation.

Several concerns need to be addressed, including the fact that the use of multiple electrodes increases the risk of bleeding. We found that the surgery duration could be shortened with the use of a single channel. This is important for both surgeon and patient. We believe this would reduce the brain shift.

The use of single electrode could also provide better motor results. There was a significant improvement in the tremor in the studied patients, which resulted in a good UPDRS. We have seen these results over the course of a long follow-up period (2–7 years).

In addition, the use of single electrodes decreases deterioration in neuropsychological functions and reduces the risks of complication, such as severe hematomas. Moreover, we think that STN does not affect the non-motor regions of the brain because the target is correctly detected.

We have seen that the clinical effect of single electrode stimulation is good even at low doses (lower stimulation intensity). We did not find any significant side effects; for this reason, we used single electrode stimulation in the majority of our cases (66.7%).

We found that most of the results from the first contact and the last contact (after many years of follow-up) are the same (73.3%). The stimulation rate of 11 patients changed, but our contact points did not change. We believe that this situation may also be indicative of improvement and stability in the clinical situation of our cases.

In the literature, the results of first year of STN-DBS for the UPDRS score and the APD reduction was better in this study (58%-60%) than the average values reported in a recent meta-analysis of the efficacy in

Table 3. Mean stimulation settings for all patients at First control and Last Control

Characteristic	First control	Last control	P value
Stimulation frequency (Hz)			
Channel L	124.9±49.4 (90–240)	128.5±52 (60–240)	ns*
Channel R	115.2±56.5 (90–240)	113.9±60.6 (60–240)	ns
Stimulation amplitude (V)			
Channel L	2.2±1.1 (1–4)	3.15±1.5 (1.5–6)	0.011
Channel R	1.8±1.03 (1–3.4)	2.58±1.37 (1.5–4.5)	0.010
Pulse width (microseconds)			
Channel L	69.0±23.7 (60–90)	68.7±23.9 (60–91)	ns
Channel R	57±25.3 (60–90)	6.73±27.9 (60–91)	ns
Medication: L-dopa (First-Last Score)			
Mean ± standard deviation	873±175.4	434.8±127.6	0.01
Range	587–1125	255–671	

ns*: not significant

treatment of advanced PD (52–56%). Our result for the UPDRS score and APD reduction was 56% and 49% respectively (15–27).

On the other hand, it is aimed to make a comparison between single-channel and multichannel MER. In particular, there should be no loss of the best target while reducing the duration of surgery and possible complications. In another particular case, the control group does not form very easily in such a study. Control group with no DBS and the patient group in single/multi-channel applications present difficulties in advanced PD patients in small number (28).

CONCLUSION

The present study was performed with a limited number of patients. There is a need for large-scale studies involving more patients and centers for better understanding of our technique. We hope that this work is innovative. However, findings of the study demonstrate that single Channel-guided STN-DBS, applied by combining imaging methods, is a safe procedure and results in improved motor outcomes.

Ethics Committee Approval: The study was approved by the Ethics Committee of Selçuk University Medical School (20.12.2017-22).

Informed Consent: There are patient approval.

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