Effect of subthalamic deep brain stimulation on levodopa-induced dyskinesia in patients with Parkinson's disease

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<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Effect of subthalamic deep brain stimulation on levodopa-induced dyskinesia in patients with Parkinson's disease

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Purpose

To evaluate the effect of bilateral subthalamic nucleus (STN) deep brain stimulation (DBS) on levodopa-induced peak dose dyskinesia in patients with Parkinson's disease (PD).

Materials and Methods

A retrospective review of patients who underwent STN DBS for PD from May 2000 to July 2012 was conducted. Only patients with levodopa-induced dyskinesia prior to surgery and more than 1 year of available follow-up data after DBS were included. The outcome measures included the dyskinesia subscore of the Unified Parkinson's Disease Rating Scale (UPDRS) part IV (item 32 to 34 of UPDRS part IV) and the levodopa equivalent daily dose (LEDD). The patients were divided into two groups based on pre- to postoperative LEDD change at 12 months after the surgery; Group 1 – LEDD decrease >15%, Group 2 – the other patients. Group 2 was further divided by the location of DBS leads.

Results

Of the 100 patients enrolled, 67 were in Group 1, while the remaining were in Group 2. Twelve months after STN DBS, Group 1 and Group 2 showed improvements of 61.90% and 57.14%, respectively in the dyskinesia subscore. Group 1 was more likely to experience dyskinesia suppression; however, the association between the groups and dyskinesia suppression was not statistically

significant (p = 0.619). In Group 2 dyskinesia was significantly decreased by stimulation of the area above the STN in 18 patients compared to stimulation of the STN in 13 patients (p = 0.048).

Conclusion

Levodopa-induced dyskinesia is attenuated by STN DBS without reducing the levodopa dosage.

Key words : deep brain stimulation, dyskinesias, Parkinson's disease, subthalamic nucleus

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I. INTRODUCTION

In 1995, the first patients with Parkinson's disease (PD) undergoing deep brain stimulation (DBS) of the bilateral subthalamic nucleus (STN) were described.[1] Currently STN DBS is an accepted surgical treatment for the control of PD symptoms inadequately controlled by medical therapies.[2-5] Numerous studies, including randomized controlled trials, have demonstrated that this procedure can dramatically improve cardinal parkinsonian symptoms such as tremor, rigidity, and bradykinesia. It has also been demonstrated to improve levodopa-induced dyskinesia and reduce the required levodopa dosage for symptom control.[2,3,6,7] Levodopa-induced dyskinesia is a frequent and important cause of disability in PD and a major reason to recommend surgical treatment. In the literature, bilateral STN DBS causes a significant reduction of dyskinesia (60 to 80%) in most patients.[8-18] Relief from dyskinesia after STN DBS has hypothesized to be due to a postoperative reduction of dopaminergic medication;[2,7,19-22] however, some data suggests that STN DBS may also have direct dyskinesia-suppressing qualities. The objective of this study was to evaluate the effects of bilateral STN DBS on levodopa-induced dyskinesia in

patients with PD after surgery, while taking into account levodopa dosage reductions.

II. MATERIALS AND METHODS

Patients

We retrospectively reviewed medical records of patients with PD who underwent bilateral STN DBS at our institution between May 2000 and July 2012. Patients with PD who suffered from severe levodopa-induced peak -dose dyskinesia before surgery were included. Patients who previously underwent thalamotomy or pallidotomy which may suppress dyskinesia, or those who had no postsurgical follow-up for a period of 12 months were excluded. Among 137 patients with PD, 100 were included in the study.

Neurosurgical Procedure

Under local anesthesia, implantation of the DBS electrodes was performed bilaterally in all patients using a Leksell stereotactic frame and magnetic resonance imaging (MRI) (Philips MR System Achieva, Eindhoven, The Netherlands)-guided targeting with Surgiplan (Elekta, Stockholm, Sweden). Initial values for STN localization were 12 mm lateral, 2 mm posterior, and 4 mm inferior to the mid-point between the anterior commissure and posterior commissure. Single-track microelectrode recording (MER) using the Microdrive System (Medtronic, Inc., Minneapolis, MN) was performed and cell activity was recorded starting from 15 mm above the STN target. After the precise localization of the target point, DBS electrodes (Medtronic 3387; Minneapolis, Minn., USA) with 4 contact points were placed in such a way that the tip of the electrode was located on the ventral boundary of the STN passing through the center of the STN. Each contact of the DBS electrode was 1.5 mm long and the contacts were 1.5 mm apart from each other. Based on the MER

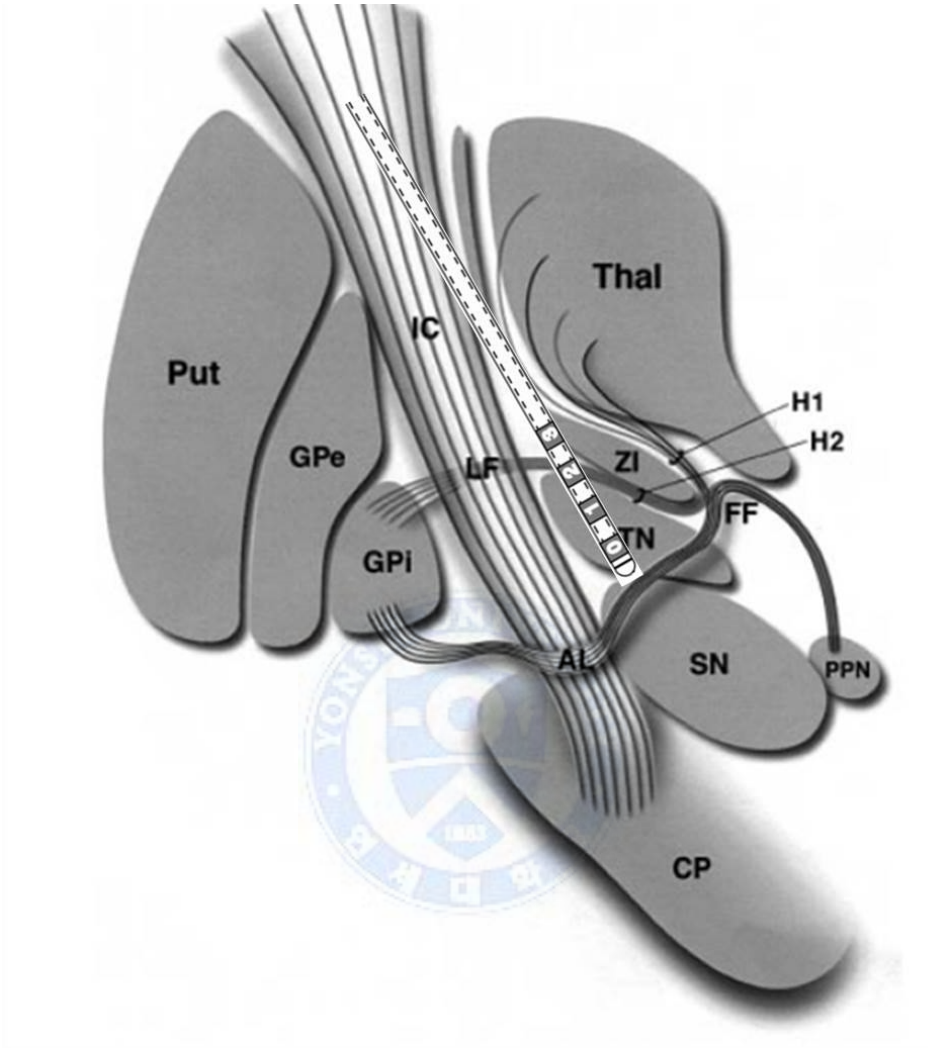


Figure 1. Schematic illustration of the electrode insertion site as described in Hamani et al.[23] The 0 and 1 contacts are located in the STN, whereas the 2 and 3 contacts are located in the area above the STN including the zona incerta. AL = ansa lenticularis; CP = cerebral peduncle; FF = Field of Forel; GPe = globus pallidus externus; GPi = globus pallidus internus; H1 = H1 Field of Forel (thalamic fasciculus); IC = internal capsule; LF = lenticular fasciculus (H2); PPN = pedunculopontine nucleus; Put = putamen; SN = substantia nigra; STN = subthalamic nucleus; Thal = thalamus; Zi = zona incerta.

results, electrodes were positioned and labeled as follows: 0 and 1, STN; 2 and 3, the area above the STN (Fig. 1). After satisfactory outcomes during test stimulations, the position of the electrode was verified by postoperative MRI, or computed tomography, that was merged with the preoperatively planned target and trajectory. If the actual electrode position was acceptable, the DBS electrodes were connected to an implantable pulse generator (IPG) placed in the subclavicular area under general anesthesia. The patients underwent a single-stage operation in which both DBS electrode insertion and IPG implantation were performed on the same day. An efficacy test was performed about 1 month after surgery. Over the next 1-2 month, the contact and stimulation parameters were optimized to obtain maximum clinical benefit and minimal side effects.

Clinical Evaluation

The outcome assessments consisted of the Unified Parkinson's Disease Rating Scale (UPDRS) part III, UPDRS part IV, and the dyskinesia subscore of the UPDRS part IV (item 32 to 34 of UPDRS part IV) before surgery and at 12 months postoperatively. The UPDRS part III was determined in both the on-medication and off-medication states. The off-state was defined as the motor condition at 8-9 a.m. after at least 12 hours of overnight withdrawal from anti-parkinsonian medication, while the on-state was defined as the maximum improvement following a dose of levodopa equal to 150% of the patient's usual first morning dose. The UPDRS part IV and the dyskinesia subscore of the UPDRS part IV were assessed in the on-medication condition during the week prior to surgery. After implantation of the DBS device all scores were assessed in the simulator-on condition. Additional information on the levodopa equivalent daily dose (LEDD) was obtained, before surgery and at 12 months postoperatively. The LEDD was calculated as follows: 100 mg standard

levodopa = 133 mg of controlled-release levodopa = 10 mg bromocriptine = 1 mg pergolide = 1 mg pramipexole = 5 mg ropinirole.

The patients were divided into two groups based on the change in between their preoperative and 12 months postoperative LEDD: Group 1 – a LEDD decrease >15%, Group 2 – the other patients.

All scores from the preoperative and 12 month postoperative state were compared to assess improvement between Group 1 and 2. The DBS electrode contact used in each Group 2 patient was also determined without reducing the LEDD. The location of each DBS contact was determined in relation to the anterodorsal boundary of the STN, which was identified by intraoperative electrophysiological mapping.

Statistical Analysis

The Student t-test was used to determine whether the mean score changes differed between Group 1 and Group 2. The Mann-Whitney U-test was used to determine whether the mean improvement of dyskinesia differed between the patients with stimulation of the area above the STN and the patients with stimulation to the STN itself. All statistical analyses were performed using SPSS (version 18.0, SPSS, Chicago, IL, USA). Mean values ± standard deviation are presented; p values <0.05 were considered statistically significant.

This study was approved by the Institutional Review Board of the local Hospital (IRB No. 4-2013-0182).

III. RESULTS

The patient demographics and clinical characteristics are described in Table 1. Of the 100 patients recruited, 67 were in Group 1 and 33 in Group 2. The mean ages of the patients at surgery were 55.82 and 58.70 years in Groups 1 and 2, respectively. The mean duration of disease before the operation was 11.13 years

Table 1. Clinical characteristics of patients

Characteristic	Group 1	Group 2	p value
No. of patients	67	33	
Male:Female	34:33	11:22	
Age at surgery (years)*	55.82 ± 9.08	58.70 ± 8.86	0.964
Disease duration (years)*	11.13 ± 4.66	11.55 ± 5.15	0.496

* Presented as mean ± standard deviation.

for Group 1 and 11.55 years for Group 2. There were no significant differences in patient demographics between the two groups.

At 12 months after STN DBS, the off-medication motor score (UPDRS part III) significantly decreased by 29.19% for Group 1 and 22.32% for Group 2. The on-medication motor score slightly decreased by 8.95% in Group 1, whereas in Group 2 it increased by 5.12%. There were no significant differences in the mean motor score changes between the groups in the on-medication ($p = 0.276$) and off-medication state ($p = 0.123$). The mean improvement of the UPDRS part IV score for Group 1 and Group 2 after 12 months were 23.25% and 23.17%, respectively. No differences were observed in the mean UPDRS part IV score changes between the groups ($p = 0.993$). The dyskinesia subscores were 4.30 ± 2.43 at baseline and 1.87 ± 2.52 at 12 months after surgery in Group 1, as compared with 4.33 ± 2.78 and 1.85 ± 2.31 in Group 2. Mean dyskinesia subscore changes after 12 months were 61.90% and 57.14% for Groups 1 and 2, respectively. Group 1 was more likely to have an improvement of dyskinesia than Group 2. However, the difference in dyskinesia improvement between the groups was not statistically significant ($p = 0.619$) (Table 2).

Analysis of Group 2 revealed that 18 patients had an active contact above the STN, including within the zona incerta, and 15 patients had an active contact within the STN. The mean improvement of the dyskinesia subscores in patients with stimulation above the STN and within the STN after 12 months were 73.57% and 37.44%, respectively. Dyskinesia was significantly attenuated by stimulation of the area above the STN in 18 patients compared to stimulation of the STN in 15 patients ($p = 0.048$) (Fig. 2).

IV. DISCUSSION

In this study, levodopa-induced peak-dose dyskinesia was reduced following bilateral STN DBS in all groups. This clearly shows that bilateral STN DBS can

Table 2. Patient outcomes

	Baseline		12 months after surgery		Mean improvement in score (%)		
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	p value
UPDRS* III (Off)†	41.55 ± 13.90	41.97 ± 12.98	28.00 ± 12.16	31.27 ± 13.96	29.19 ± 27.40	22.32 ± 33.45	0.276
UPDRS* III (On)†	19.64 ± 9.51	16.67 ± 9.01	18.01 ± 9.11	18.85 ± 11.28	8.95 ± 39.95	-5.12 ± 47.59	0.123
UPDRS* IV†	8.13 ± 4.41	6.97 ± 3.85	5.79 ± 3.36	4.85 ± 3.82	23.25 ± 42.97	23.17 ± 48.79	0.993
Dyskinesia subscore†	4.30 ± 2.43	4.33 ± 2.78	1.87 ± 2.52	1.85 ± 2.31	61.90 ± 42.67	57.14 ± 49.17	0.619
LEDD§†	1120.54 ± 460.76	746.74 ± 407.01	402.31 ± 284.04	828.48 ± 368.41	62.31 ± 22.59	-23.08 ± 52.41	0.000

*UPDRS, Unified Parkinson's Disease Rating Scale.

§LEDD, Levodopa equivalent daily dose.

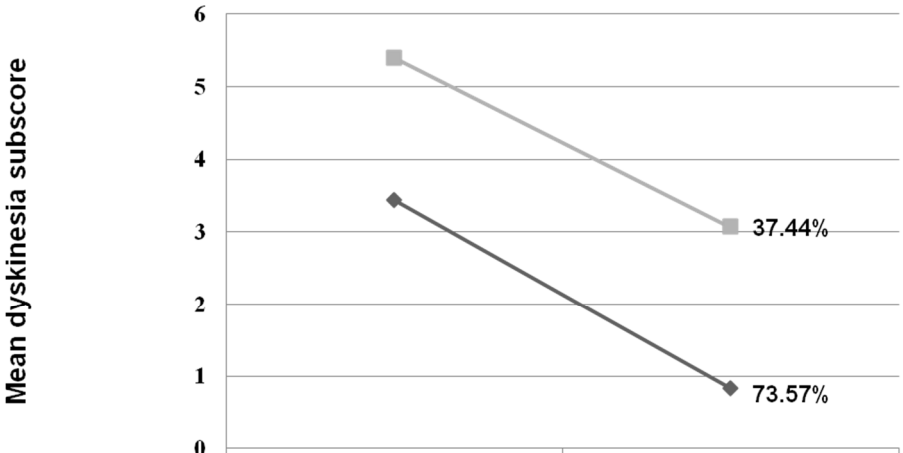
† Presented as mean ± standard deviation.

be a good therapeutic option for the treatment of dyskinesia.

Previous studies have also reported an improvement of levodopa-induced peak-dose dyskinesia following bilateral STN DBS. A randomized controlled trial by Odekerken et al. demonstrated that the severity of on-phase dyskinesia, as assessed by the clinical dyskinesia rating scale (CDRS, range 0-28), showed profound and significant changes from baseline (4.8) to 12 months after STN DBS (3.8).[6] They noted that the levodopa dosage was reduced from 1254 mg/day preoperatively to 708 mg/day postoperatively. Another study by Portman et al. reported that the severity of on-medication dyskinesia clearly improved by 57% 12 months after STN DBS.[2] They noted that surgery resulted in a marked reduction of anti-parkinsonian medication (-39%) and consequently reduced the severity of peak-dose dyskinesia dramatically.

There has been some discussion regarding the mechanisms underlying the effect of STN DBS on levodopa-induced dyskinesia in patients with PD. The majority of researchers opine that the significant postoperative reduction of dyskinesia is caused by a significant postoperative reduction of levodopa medication.[2,7,19-22]

In contrast to previous studies, the results of this study demonstrated that dyskinesia was improved even though the medication was unchanged, or increased, after surgery. Importantly, in PD patients with STN DBS, the improvement in dyskinesia (~70%) is larger than the reduction in levodopa dose (35-40%) unlike for other complications. Only case reports and small series have been published about the direct effect of STN DBS on levodopa-induced dyskinesia (Table 3). Krack et al. reported that high-frequency stimulation of the STN reduced the severity of peak-dose dyskinesia by 30% in response to a suprathreshold dose of levodopa.[24] Ostergaard et al. described an 86% reduction in the duration of dyskinesia 12 months after bilateral STN DBS.[3] In their study, daily levodopa dose equivalents were reduced only by 19%, which is a smaller reduction in the dose of daily levodopa equivalents than in other similar studies. Katayama et al. analyzed the direct effect of STN DBS on peak-dose dyskinesia



	Baseline	12 months after surgery
above the STN stimulation	3.44	0.83
within the STN stimulation	5.40	3.07

Figure 2. The mean improvement of dyskinesia was reduced by 73.57% (from 3.44 preoperatively to 0.83 postoperatively) in patients with stimulation of the area above the STN, whereas the mean improvement of dyskinesia was reduced by only 37.44% (from 5.40 preoperatively to 3.07 postoperatively) in patients where the STN was directly stimulated. There was a significant difference between stimulation of the area above the STN and of the STN.

during a 2-week period after surgery without reducing the levodopa dosage.[25] They noted that the peak-dose dyskinesia was quickly attenuated by bipolar stimulation in 8 (18%) of the 45 patients. Combining our findings with those of the aforementioned studies, improvement of levodopa-induced dyskinesia could be related directly to the effect of bilateral STN DBS.

It has been difficult to demonstrate a role for the STN in the cancellation of dyskinesia beyond the reduction in daily levodopa dose in patients. Several explanations could account for the direct antidyskinetic effect of STN DBS on levodopa-induced dyskinesia. First, most studies suggested that stimulating pallidothalamic, pallidosubthalamic, or subthalamopallidal fibers, which are densely distributed above the STN, can cause effects similar to those of thalamic or pallidal DBS.[8,25-27] In particular, the lenticular fasciculus, which lies between the STN inferiorly and the zona incerta superiorly, is a white matter tract from the dorsal globus pallidus interna (GPi). This tract transverses the internal capsule and then combines with the ansa lenticularis (the ventral GPi outflow tracts) to form the thalamic fasciculus in the field H_1 of Forel, which then terminates at the ventroanterior/ventrolateral (VA/VL) thalamic nuclei.[8,28,29] Therefore, modulation of these fibers may induce an effect similar to that of GPi DBS or Forel's field surgery. The results of this study also revealed larger improvements in dyskinesia with stimulation of the area above the STN compared with stimulation of the STN itself, which is consistent with previous findings.[25] Second, some authors have indicated that the antidyskinetic response after STN DBS could be attributed to the effect of continuous high-frequency electrical stimulation in the target.[22,24,30] Thus, STN surgery could induce a stable and continuous functional state with reduced fluctuations in basal ganglia activity, which mimics the effect of continuous dopamine stimulation as in during the infusion of dopamine receptor agonists.[24,31,32] Krack et al. described the effect of chronic high-frequency stimulation of the STN on peak-dose dyskinesia as being related directly to the functional inhibition of the

Table 3. Comparison of studies of subthalamic deep brain stimulation on levodopa-induced dyskinesia in patients with Parkinson's disease

Author, year of publication	Patients	Improvement in dyskinesia
Mendez R et al. 1999[35]	68-year-old patient	The dyskinesia score was 15 when the stimulation was off, and reduced immediately to 2 when the stimulation was switched on. The anti-parkinsonian therapy was maintained.
Krack et al. 1999[24]	8 patients	The severity of peak-dose dyskinesia was reduced by 30% using the same suprathreshold dose as before the operation.
Ostergaard et al. 2002[3]	26 patients	The results showed a significant reduction of 86% in duration of dyskinesia. Daily levodopa dose equivalents were reduced only by 19%.
Katayama et al. 2006[25]	45 patients	Almost complete control of the peak-dose dyskinesia was observed in 24 (53%) of the 45 patients without reducing the levodopa dosage during the early period after surgery.
J. Herzog et al. 2007[8]	3 patients	In 2 of 3 patients, additional stimulation of a proximal contact located within the subthalamic white matter may lead to a significant reduction of dyskinesia associated with STN DBS.
Nishikawa Y et al. 2010[26]	71-year-old patient	Using contact 2 as the cathode, levodopa-induced dyskinesia was markedly attenuated. The patient received the same doses of anti-parkinsonian drugs as preoperatively.
Oyama G et al. 2012[36]	75 patients	11.9% of STN DBS subjects had dyskinesia suppression despite no change in medication.

STN and indirectly to the replacement of the pulsatile dopaminergic stimulation by continuous functional inhibition of the STN.[24] The results of their study are supported by previous observations from Nimura et al. who measured synaptic dopamine levels in the striatum using positron emission tomography with [^{11}C]raclopride.[33] They reported that DBS of the STN induces the stabilization of synaptic dopamine concentrations in the striatum and may contribute to the alleviation of levodopa-related motor fluctuations. A third possible mechanism is related to a dopaminergic bundle that courses through the anatomic space in between the zona incerta and the STN, which travels along the lenticular fasciculus caudally and the ansa lenticularis rostrally.[28,34] Direct stimulation of this bundle could result in an anti-dopaminergic effect by a depolarization blockage of the axons.[28]

V. CONCLUSION

In conclusion, this study confirms the efficacy of STN DBS in ameliorating levodopa-induced dyskinesia in PD whether the levodopa dosage was reduced. Further, the improvement in levodopa-induced dyskinesia following stimulation of the area above the STN was larger than that after stimulation of the STN. Thus, we would like to try simultaneous stimulation of both the STN and the area above the STN for diminishing both the cardinal symptoms of PD and levodopa-induced dyskinesia. This combined stimulation could be possible using a single quadripolar electrode.

Although this was an unblinded retrospective study, it supports findings from previous studies investigating direct dyskinesia suppression by STN DBS. Further studies on the direct antidyskinetic effect of STN DBS in larger groups are needed to investigate the mechanism of STN DBS in patients with levodopa-induced dyskinesia.

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ABSTRACT(IN KOREAN)

파킨슨 병 환자에서 발생한 레보도파에 의해 유발된 이상운동증에 대한 시상하핵 뇌심부자극술의 효과

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배경 및 목적

파킨슨 병 환자에서 발생한 레보도파에 의해 유발된 이상운동증에 대한 양측 시상하핵 뇌심부자극술의 효과를 평가하기 위함이다.

재료 및 방법

2000년 5월부터 2012년 7월까지 파킨슨 병으로 시상하핵 뇌심부자극술을 시행받은 환자를 후향적으로 검토하였다. 수술 전 레보도파에 의한 이상운동증을 가진 환자와 뇌심부자극술 이후 1년 이상 추적관찰을 시행한 환자를 선정기준으로 하였다. 결과는 이상운동증 점수 (통합형 파킨슨병 평가척도 32, 33, 34번 항목의 합계)와 레보도파 용량으로 평가하였다. 환자는 수술 전과 수술 후 12개월째 레보도파 용량 변화를 기준으로 두 그룹으로 나누었다. 그룹 1은 수술 전후 레보도파 용량 변화가 15% 를 넘는 환자이며, 그룹 2는 나머지 환자들이다. 그룹 2에 포함된 환자는 전극의 위치에 따라 다시 두 그룹으로 나누었다.

결과

총 100명의 환자 중 그룹 1에는 67명, 그룹 2에는 33명이 포함되었다. 수술 후 12개월째 그룹 1, 2의 이상운동증은 각각 61.90%, 57.14% 호전되었다. 그룹 1에서 이상운동증의 억제효과가 큰 것 같으나, 두 그룹 사이에 이상운동증 억제효과에 대한 통계적 차이는 보이지 않았다. (p = 0.619). 그룹 2에서 시상하핵 배측 부분을 자극한 18명의 환자에서 시상하핵 내를 자극한 13명의 환자에서보다 이상운동증이 의미있게 감소하였다. (P = 0.048)

결론

레보도파에 의한 이상운동증은 레보도파 용량을 줄이지 않고도 시상하핵 뇌심부자극술에 의해서 억제될 수 있다.

핵심되는 말 : 뇌심부자극술, 이상운동증, 파킨슨 병, 시상하핵