An 8-Year Follow-up on the Effect of Subthalamic Nucleus Deep Brain Stimulation on Pain in Parkinson Disease

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IMPORTANCE Pain is a common and distressing feature in Parkinson disease (PD). The major indication of subthalamic nucleus deep brain stimulation (STN DBS) is motor complications in advanced PD; however, pain reduction after STN DBS has been noted.

OBJECTIVE To evaluate the long-term effect of STN DBS on pain in PD.

DESIGN, SETTING, AND PARTICIPANTS Twenty-four patients who underwent STN DBS at the Movement Disorder Center at Seoul National University Hospital from June 1, 2005, through March 31, 2006, were studied. The assessments of pain were performed preoperatively and 8 years after surgery. Because 13 of the total 24 patients had additional 2-year postoperative data, the serial change between the preoperative and the 2- and 8-year follow-ups after surgery was also evaluated.

MAIN OUTCOMES AND MEASURES Motor symptoms were assessed using the Unified Parkinson’s Disease Rating Scale and the Hoehn and Yahr staging scale. The severity of pain was scored according to an ordinal scale ranging from 0 (absent) to 10 (maximal pain) in 7 parts of the body (head, neck, trunk, and the upper and lower extremities on each side of the body). For each body part, the quality of pain was grouped into 1 of 4 categories: dystonic, musculoskeletal, radiculoneuritic, and central.

RESULTS Sixteen of the 24 patients (67%) experienced pain at baseline when not taking medication (off-state). All off-state pain at baseline improved or disappeared at 8 years after surgery. The number of body parts with pain was 21 at baseline and decreased to 11 at 8 years after the surgery. The mean (SD) and median scores of the off-state pain were 6.2 (2.5) and 7.0 at baseline and improved to 3.5 (2.2) and 2.5 at 8 years after the surgery, respectively. However, new pain developed in 18 of 24 patients (75%) during the 8-year follow-up period. The number of body parts with newly developed pain was 47, and the mean (SD) and median scores for new pain were 4.4 (3.0) and 3.0, respectively. The types of new pain at 8 years were musculoskeletal in 11 patients, central in 4 patients, radiculoneuritic in 3 patients, and dystonic in 1 patient.

CONCLUSIONS AND RELEVANCE Pain associated with PD is improved by STN DBS, and the beneficial effect persists after a long-term follow-up of 8 years. In addition, new pain, especially the musculoskeletal type, developed in most patients, becoming a long-term distressing problem.
Pain is a common and distressing nonmotor symptom in Parkinson disease (PD). Several studies have found that 40% to 85% of patients with PD have pain, and pain associated with PD is negatively associated with quality of life. Improving pain is therefore an important concern in the management of PD.

Pain in PD can be classified into 2 types: PD-related pain, which is caused or aggravated by PD, and PD-unrelated pain. Both types of pain are known to respond to medical and surgical treatments that target the motor symptoms of PD. However, the effect and mechanism of dopaminergic medication on pain in PD are not fully understood. Some studies have reported that levodopa increased the pain threshold and tolerance in patients with PD. Although subthalamic nucleus deep brain stimulation (STN DBS) has been used as another treatment option for motor symptoms in PD, its effects are not limited to motor symptoms and the pain-reducing effect of STN DBS is gaining attention. A previous study reported that high-dose levodopa is inferior to STN DBS for the relief of pain.

We previously presented the results of follow-up studies on the beneficial effect of STN DBS on patients with advanced PD. In the initial study, a 3- to 6-month postoperative evaluation was performed in 29 patients, and most of them reported an improvement in pain, especially when they were not taking the medication. The next follow-up study in 21 of these 29 patients revealed that this beneficial effect persisted after 24 months. In addition, we found that new pain developed in many patients during the 3- to 6-month and 24-month follow-up periods.

Although the short-term benefits of STN DBS on pain in patients with PD have been documented, the long-term outcomes of the procedure are unknown. We report the 8-year postoperative follow-up of 24 patients following our previous studies.

Methods

Patients
This study included 24 patients (15 men and 9 women) who underwent STN DBS at the Movement Disorder Center (MDC) at Seoul National University Hospital from June 1, 2005, through March 31, 2006. The inclusion criteria for STN DBS were a clinical diagnosis of idiopathic PD, levodopa responsiveness with severe motor complications, no severe dementia, and normal findings on brain magnetic resonance imaging. Although we initially investigated 34 patients (including 29 from our first previous study), 4 patients died of old age, and 6 patients were excluded from this study because it was impossible for them to complete the questionnaire by themselves due to cognitive impairment or general deconditioning. The remaining 24 patients followed the scheduled protocol at the MDC, which was approved by the Seoul National University Hospital Institutional Review Board and conformed to the principles of the Declaration of Helsinki.

Surgical Procedures
The STN DBS implantation was performed as previously described. After the surgery, the exact locations of the electrodes and contacts were verified using a computed tomography–magnetic resonance imaging fusion technique. The stimulation settings were adjusted individually to optimize the clinical conditions. Bilateral surgery was performed on all patients except for 3 patients who had highly asymmetric motor symptoms and underwent unilateral surgery contralateral to the more severe symptomatic side.

Clinical Assessments
Preoperative and postoperative evaluations were performed according to the previously described MDC protocol. All patients were admitted to the MDC for preoperative evaluations over a period of 3 days. Motor symptoms were videotaped and assessed using the Unified Parkinson’s Disease Rating Scale (UPDRS) part III and the Hoehn and Yahr staging scale when taking (on-state) and not taking (off-state) medication. The off-state was defined as the motor condition at 8 to 9 AM after at least 12 hours of overnight withdrawal from antiparkinsonian medications, and the on-state was defined as the maximum improvement after the usual first morning medication. Parkinsonian motor symptoms were regarded as asymmetrical when a difference in the off-state motor UPDRS scores between the more affected and less affected sides was greater than 4 points. Additional data on the duration of the disease and the prescribed dose of levodopa and other antiparkinsonian drugs were obtained. The levodopa equivalent daily dose was calculated as previously described.

All patients were asked for a detailed evaluation of their pain during the previous week. Any type of pain, irrespective of its presumptive cause, was recorded. The severity of pain was scored according to an ordinal scale ranging from 0 (absent) to 10 (maximal pain) in 7 parts of the body (head, neck, trunk, and the upper and lower extremities on each side of the body). For each body part, the quality of pain was described by the patients, and each pain was grouped into 1 of 4 categories according to the classification proposed by Ford as follows: dystonic, musculoskeletal, radiculoneuritic, and central. Dystonic pain is associated with dystonic movements and postures and has been described as off-period dystonia or painful dystonic spasms. Musculoskeletal pain includes aching, cramping, and arthralgic and myalgic sensations in the joints and muscles. Radiculoneuritic pain is well localized to the territory of the nerve root or root. Central pain is described as a bizarre, unexplained sensation of burning, scalding, or formication that is usually poorly localized. The origin is likely to be the central nervous system, including the basal ganglia. Akathisia is defined as inner restlessness, often accompanied by an urge to move. Akathitic discomfort was not included in this study because it was not regarded as a painful sensation by the patients. In patients with motor fluctuations, the on-state pain and the off-state pain were recorded separately. The pain was considered fluctuating when the score of the off-state was greater than that of the on-state or when the pain existed only in the off-state. All 24 patients were evaluated preoperatively and 8 years after surgery. Because 13 (7 men and 6 women) of the 24 patients were also included in our previous study on the 2-year postoperative follow-up after DBS, we had data on pain at the 2-year follow-up for those patients, and a subgroup analysis was performed to evaluate the serial change between the preoperative and the 2-
and 8-year follow-ups after surgery. The postoperative off-state pain was compared with the preoperative off-state pain. When the off-state pain disappeared after the surgery, the motor state of the patient was regarded as on-state pain, and the postoperative pain was compared with the preoperative off-state pain. In patients who stopped taking dopaminergic medication after surgery, postoperative pain was compared with the preoperative off-state pain.

Results

Baseline Characteristics

Table 1 presents the baseline characteristics of the patients. Although 3 of 24 patients initially underwent unilateral surgery, all 3 patients were considering surgery on the second side because of worsening of ipsilateral motor symptoms within 2 years.25

Preoperative Assessment of Pain

Sixteen of the 24 patients (67%) experienced off-state pain at baseline. Thirteen patients reported pain in more than one part of the body. On average, the patients experienced pain in 3 parts of the body. The most common body parts with pain were the lower extremities, and central pain was the most prevalent type. The mean (SD) and median off-state pain scores were 6.2 (2.6) and 6.5, respectively. The mean (SD) and median scores of dystonic and central pain were higher (6.3 [2.7] and 5.0) and 6.2 [2.5] and 7.0, respectively) than those of radiculoneuritic (6.0 [0.0] and 6.0, respectively) and musculoskeletal pain (5.9 [3.3] and 6.0, respectively). Headache was reported by 3 patients, with mean and median pain scores of 5.7 and 5.0, respectively. Of the 9 patients with asymmetrical PD, 1 reported more pain on the side ipsilateral to the more severe parkinsonism, and 2 had bilateral symmetrical pain. The remaining 6 patients had no pain.

All 16 patients with preoperative off-state pain experienced more severe pain in the off-state than in the on-state except for 1 patient. In that patient, the mean score for radiculoneuritic pain in the lower extremities was 7 in the on-state and 6 in the off-state. The number of body parts with off-state pain was reduced from 48 to 29, and the mean (SD) and median pain scores improved from 6.2 (2.6) and 6.5 to 3.4 (1.9) and 3.0, respectively, after medication. Of the 16 patients with off-state pain at baseline, 12 had fluctuations in pain with motor symptoms, including 6 patients who reported complete disappearance of pain in the on-state. When only these 12 patients with preoperative fluctuating pain were counted, the number of body parts with off-state pain was reduced from 43 to 18, and the mean (SD) and median pain scores improved from 6.3 (2.6) and 7.0 to 2.6 (1.5) and 2.3, respectively, after medication.

Postoperative Assessment of Pain

The body distribution, quality, and severity of off-state pain in all 24 patients are presented in Table 2. Twenty of 24 patients (83%) had off-state pain at 8 years after surgery. Among the 20 patients, 9 had motor fluctuations, and 4 reported fluctuations in pain with motor symptoms. In those 4 patients, 1 experienced severe (mean pain score of 10) dystonic pain in the off-state, and 1 who had only on-state pain before surgery reported complete disappearance of on-state pain; however, musculoskeletal and central pain were newly developed in the off-state. At 8 years postoperatively, the off-state pain in all 12 patients who had preoperative fluctuating pain was improved in whole or in part. However, there was also a worsening of the preoperative off-state dystonic pain in 2 patients and musculoskeletal pain in 1 patient. Nonfluctuating pain was experienced by 4 patients at baseline and improved at 8 years after surgery in all of them. In this manner, STN DBS improved the fluctuating and nonfluctuating pain even 8 years after surgery.

As described in Figure 1A, the mean (SD) and median pain scores of dystonic pain were aggravated from 6.3 (2.7) and 5.0 at baseline to 8.5 (1.6) and 8.5, respectively, at 8 years after surgery. However, this 8-year score was a mean value, including the scores of 2 patients who had severe off-state dystonic pain due to rigidity, and the remaining patients had no dystonic pain. In terms of severity, the total off-state pain score was reduced by 55% for radiculoneuritic, 44% for central, and 29% for musculoskeletal pain compared with preoperative scores.

Despite the improvement in preoperative off-state pain, many patients reported new pain in the follow-up period. Body
The number of patients with off-state pain for each category of pain and all pain for the total group (N = 24) at baseline and 8 years after surgery (A) and the subgroup (n = 13) at baseline, 2 years after surgery, and 8 years after surgery (B). The numbers above the columns indicate the mean off-state pain score.

distributions of the off-state pain indicating newly developed pain compared with the baseline are presented in the eTable in the Supplement. At 8 years, new pain developed in 18 of 24 patients (75%), including 5 who experienced no pain at baseline. The number of body parts with newly developed pain was 47, and the most common body parts were the lower extremities followed by the upper extremities. The mean (SD) and median scores for new pain were 4.4 (3.0) and 3.0, respec-
Table 3. Body Distribution, Quality, and Severity of Off-State Pain in a Subgroup of 13 Patients*

<table>
<thead>
<tr>
<th>Body Part</th>
<th>Total</th>
<th>Dystonic</th>
<th>Central</th>
<th>Musculoskeletal</th>
<th>Radiculoneuritic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 2 y 8 y</td>
<td>Baseline 2 y 8 y</td>
<td>Baseline 2 y 8 y</td>
<td>Baseline 2 y 8 y</td>
<td>Baseline 2 y 8 y</td>
</tr>
<tr>
<td>Neck</td>
<td>4 (8.6, 8.3)</td>
<td>1 (4.0, 4.0)</td>
<td>1 (4.0, 4.0)</td>
<td>2 (9.3, 9.3)</td>
<td>NA</td>
</tr>
<tr>
<td>Trunk(Stomach)</td>
<td>4 (6.0, 6.3)</td>
<td>2 (4.3, 4.3)</td>
<td>6 (5.0, 5.0)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Arm</td>
<td>6 (7.2, 8.5)</td>
<td>4 (2.0, 2.0)</td>
<td>8 (3.5, 2.0)</td>
<td>2 (3.0, 3.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Leg</td>
<td>19 (6.7, 7.5)</td>
<td>8 (4.3, 4.5)</td>
<td>15 (3.3, 2.5)</td>
<td>6 (8.8, 8.5)</td>
<td>NA</td>
</tr>
<tr>
<td>No. of body parts with pain</td>
<td>33 (6.9, 7.8)</td>
<td>15 (3.6, 4.0)</td>
<td>30 (3.7, 3.0)</td>
<td>8 (7.6, 8.0)</td>
<td>0</td>
</tr>
<tr>
<td>No. of patients with pain</td>
<td>11</td>
<td>5</td>
<td>11</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.
*The numbers in each cell indicate the number of body parts with pain. Mean and median pain scores are in parentheses.

Discussion

The principle finding of this study is that the beneficial effects of STN DBS on pain in PD persisted after a long-term follow-up period of 8 years. All off-state pain at baseline improved or disappeared at 8 years after surgery. In addition, STN DBS was effective on nonfluctuating pain, which did not respond to dopaminergic medication, and fluctuating pain. Except for 2 patients who had severe dystonic off-state pain with rigidity, dystonic pain was the most responsive to STN DBS, followed by radiculoneuritic (55%), central (44%), and musculoskeletal (29%) pain in terms of pain severity. However, we cannot state that STN DBS is effective in radiculoneuritic pain because the number of patients with radiculoneuritic pain increased from 1 at baseline to 4 at 8 years after surgery. Another important finding is that new pain developed in most of the patients during the 8-year follow-up period. The number of body parts with pain increased from 48 at baseline to 60 at 8 years. However, the mean (SD) and median pain scores improved from 6.2 (2.6) and 7.5 at baseline to 4.8 (2.0) and 4.8 at 8 years postoperatively, respectively. The changing aspects for total pain and each category of pain in all patients are illustrated in Figure 2. The results of the present study were nearly consistent with those of our previous study on the 2-year follow-up.

Most of the new pain that developed during the 8-year follow-up period was the musculoskeletal type, which was also the most common at 8 years postoperatively. Musculoskeletal pain is defined as an aching and cramping sensation of the joints or muscles. Because it has been commonly believed to result from rigidity and akinesia associated with PD, the prevalence of musculoskeletal pain was higher in the PD group than in the controls. The musculoskeletal pain in PD was worsened by immobility, and it promoted the immobility at the same time, resulting in the aggravation of parkinsonian motor symptoms and deterioration in the quality of life. Because musculoskeletal pain does not readily respond to the medical and surgical treatment of PD, treatment of its underlying cause should be considered. In our center, it was reported that musculoskeletal problems were important causes of functional impairment at 3 years postoperatively in patients undergoing STN DBS. The results of the present study highlight once again that musculoskeletal problems should be considered when predicting the operative outcome before surgery, and continuous evaluation and treatment of musculoskeletal pain should be performed after surgery.
Despite the progression of PD itself with the passage of time, there was remarkable improvement in central pain during the 8 years. A total of 9 patients had central pain preoperatively, and 5 patients had central pain 8 years later. The number of body parts with pain was 21 at baseline and decreased to 11 at 8 years after the surgery. Mean (SD) and median scores of off-state pain were 6.2 (2.5) and 7.0 at baseline and improved to 3.5 (2.2) and 2.5 at 8 years after the surgery, respectively. Central pain is described as a bizarre, unexplained sensation of stabbing or burning, and it is referred to as a direct consequence of PD itself rather than as a result of dystonia, rigidity, peripheral neuropathy, or a musculoskeletal cause. Improvement in central pain by STN DBS suggested that there are other mechanisms in addition to reducing pain by alleviating motor symptoms, such as rigidity. This mechanism of central pain reduction by STN DBS in PD is not completely understood; however, it is considered that STN DBS alters sensory processing in the central nervous system, including the basal ganglia. Several previous studies have found that STN DBS increases the threshold of pain in PD, supporting this hypothesis.

The present study has some limitations. First, the number of patients was small, and there was no control group that was treated medically. Second, we did not evaluate the association between the score of motor UPDRS and pain. This was because the locations, qualities, and severity of pain were different in each patient, and the same pain score in the different body parts does not translate to the same degree of distress; therefore, a comparison of the simple arithmetic sum of the pain scores among patients is meaningless. Third, we did not check the overall level for pain by using a more global scoring system, such as a visual analog scale, because some patients had difficulty drawing lines because of the motor symptoms of PD. Fourth, the objective cognitive and psychological scores were not reflected in the analysis of pain, although we excluded patients who could not complete a questionnaire because of cognitive impairment.

Conclusions

We found that pain in PD is improved by STN DBS, and the beneficial effect persists after a long-term follow-up of 8 years. In addition, new pain developed in most of the patient during the 8-year follow-up period. We also found that STN DBS is decidedly less effective for musculoskeletal pain and tends to increase over time. Therefore, musculoskeletal pain needs to be addressed independently.
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Drafting of the manuscript: Jung, Jeon.
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REFERENCES