Interleaving subthalamic nucleus deep brain stimulation to avoid side effects while achieving satisfactory motor benefits in Parkinson disease

A report of 12 cases

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Abstract

Background: Deep brain stimulation (DBS) of the subthalamic nucleus is an effective treatment for advanced Parkinson disease (PD). However, achieving ideal outcomes by conventional programming can be difficult in some patients, resulting in suboptimal control of PD symptoms and stimulation-induced adverse effects. Interleaving stimulation (ILS) is a newer programming technique that can individually optimize the stimulation area, thereby improving control of PD symptoms while alleviating stimulation-induced side effects after conventional programming fails to achieve the desired results.

Methods: We retrospectively reviewed PD patients who received DBS programming during the previous 4 years in our hospital. We collected clinical and demographic data from 12 patients who received ILS because of incomplete alleviation of PD symptoms or stimulation-induced adverse effects after conventional programming had proven ineffective or intolerable. Appropriate lead location was confirmed with postoperative reconstruction images. The rationale and clinical efficacy of ILS was analyzed.

Results: We divided our patients into 4 groups based on the following symptoms: stimulation-induced dysarthria and choreoathetoid dyskinesias, gait disturbance, and incomplete control of parkinsonism. After treatment with ILS, patients showed satisfactory improvement in PD symptoms and alleviation of stimulation-induced side effects, with a mean improvement in Unified PD Rating Scale motor scores of 26.9%.

Conclusions: ILS is a newer choice and effective programming strategy to maximize symptom control in PD while decreasing stimulation-induced adverse effects when conventional programming fails to achieve satisfactory outcome. However, we should keep in mind that most DBS patients are routinely treated with conventional stimulation and that not all patients benefit from ILS. ILS is not recommended as the first choice of programming, and it is recommended only when patients have unsatisfactory control of PD symptoms or stimulation-induced side effects after multiple treatments with conventional stimulation. A return to conventional stimulation may be required if ILS induces new side effects or the needs of the patient change.

Abbreviations: DBS = deep brain stimulation, ILS = interleaving stimulation, PD = Parkinson disease, STN = subthalamic nucleus, UPDRS = Unified Parkinson Disease Rating Scale.

Keywords: deep brain stimulation, interleaving stimulation, Parkinson disease, side effects, subthalamic nucleus

1. Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective surgical treatment for advanced Parkinson disease (PD).[1] The programming technique used for DBS is an important factor affecting the outcome of PD patients. Conventional programming approaches are satisfactory for most PD patients, with limited side effects. Nevertheless, undesirable results or side effects emerge in some patients despite efforts to program the DBS device using techniques such as changing the amplitude, pulse width, and frequency, or switching to monopolar/bipolar mode. Interleaving stimulation (ILS) is a recent programming approach for optimizing the electrical field to improve PD symptoms with fewer stimulation-induced side effects. With ILS, 2 programs can be interleaved in an alternating fashion on the same lead. Each of the 2 programs can specify amplitude, pulse width, and electrode contacts. The frequency for each program is the same and is limited by the device to a maximum of 125 Hz.[2]

Studies of ILS are rare and limited to case reports. We retrospectively collected the clinical data from 12 PD patients who received ILS and analyzed the rationale and clinical efficacy of ILS.

2. Materials and methods

2.1. Patients

We retrospectively reviewed and assessed data in the medical records of PD patients who received DBS programming during
the previous 4 years in our hospital. Most DBS patients are first treated using conventional stimulation; ILS is not recommended as the first choice of programming. It is recommended only when patients have unsatisfactory control of PD symptoms or stimulation-induced side effects after multiple treatments with conventional stimulation. Of the PD patients treated in our hospital, 18 patients were switched to ILS. However, 1 patient was lost to follow-up. Of these 17 patients, 3 were excluded because they used ILS for <6 months, making evaluation of long-term benefits of ILS difficult. One patient used ILS for 4 months with satisfactory benefits; however, he switched to conventional stimulation with bipolar mode because of stimulation-induced choreoathetoid dyskinesias during the fifth month. Another patient benefited from ILS for 5 months after gait disturbance with conventional programming. Nevertheless, he decided to switch to conventional stimulation with double monopolar mode to achieve better control for rigidity of the right limbs and gave up part of the benefit regarding gait disturbance. Finally, our cohort for evaluating the long-term benefit of ILS included 12 patients. These patients had experienced stable and satisfactory clinical benefits for at least 12 months on ILS, and their clinical data were collected.

The clinical and demographic data from these patients are presented in Table 1. All patients underwent bilateral STN DBS (type 3389 electrode and Activa PC/RC implantable pulse stimulator, Medtronic, Minneapolis, MN). Unified Parkinson Disease Rating Scale motor (UPDRS-motor) score and self-evaluation were performed before and after ILS. Unsatisfactory improvement of PD symptoms was defined as failure to achieve satisfactory control of PD symptoms including motor fluctuation, tremor, rigidity, and gait disturbance. The patients also suffered from stimulation-induced side effects, including dysarthria and choreoathetoid dyskinesias, which occurred before patients had satisfactory alleviation of parkinsonism. Satisfactory outcome was defined as satisfaction on the part of both the patient and the doctor regarding the control of the undesirable results and side effects. The informed consents were obtained from the patients.

2.2. Programming techniques

Our programming was a multidisciplinary process. Standard algorithms should be used for all patients before ILS. Overall, a monopolar review was carried out for each patient at the initial programming visit to define the functionality and efficacy of each contact as well as the thresholds for side effects using standard algorithms. Each contact might have its own functional property for improving PD symptoms or inducing side effects. For example, 1 contact might readily alleviate tremor (high threshold for alleviating tremor) but induce dysarthria easily (low threshold for inducing dysarthria). The standard algorithms for DBS programming were used as the basis for choosing ILS contacts and settings for each patient. We also referred to the reconstruction images to confirm the location of postoperative leads in fused images of preoperative MRI and postoperative CT images. Based on the standard algorithms and reconstruction images, we would choose and adjust the most suitable contacts and settings for ILS for each patient to improve their PD symptoms or alleviate side effects. In addition, after ILS with 1 program, which uses the specifically chosen contacts and settings and in which the amplitude and pulse width can be gradually increased as necessary and can be monitored for efficacy and adverse effects, ILS with another program selecting other specific contacts and settings, according to standard algorithms, with increased amplitude and pulse width can be performed to achieve further motor benefit and avoid adverse effects (Fig. 1).

After ILS, the patients underwent self-evaluation and reflected upon whether they were satisfied with the programming results.

| Patient | Sex | Time of PD, y | Age at DBS | Chief complaint before ILS | Follow-up after ILS, mo | Extra side effects after ILS |
|---------|-----|---------------|------------|---------------------------|------------------------|----------------------------|
| 1       | Male| 9             | 65         | Gait disturbance          | 13                     | None                       |
| 2       | Female| 5            | 50         | Rigidity                  | 16                     | None                       |
| 3       | Female| 7            | 60         | Gait disturbance, choreoathetoid dyskinesias | 16 | None |
| 4       | Male| 9             | 57         | Gait disturbance, tremor  | 12                     | None                       |
| 5       | Male| 13           | 55         | Dysarthria                | 14                     | None                       |
| 6       | Female| 6            | 57         | Gait disturbance          | 13                     | None                       |
| 7       | Female| 12           | 51         | Dysarthria                | 14                     | None                       |
| 8       | Male| 9             | 52         | Gait disturbance, choreoathetoid dyskinesias | 14 | None |
| 9       | Male| 6             | 59         | Gait disturbance, rigidity | 19                     | None                       |
| 10      | Male| 10            | 51         | Gait disturbance, rigidity | 28                     | None                       |
| 11      | Male| 7             | 43         | Gait disturbance          | 12                     | None                       |
| 12      | Female| 8            | 58         | Choreoathetoid dyskinesias | 14 | None |

DBS = deep brain stimulation, ILS = interleaving stimulation, PD = Parkinson disease.

Figure 1. Algorithm for interleaving stimulation. ILS = interleaving stimulation, PD = Parkinson disease.
Table 2

Final stereotactic coordinates*.

| Patient | Right lead (X, Y, Z) | Left lead (X, Y, Z) |
|---------|---------------------|--------------------|
| 1       | 13, 3.2, 5.9        | 13.7, 4.2, 4.0     |
| 2       | 12.8, 1.5, 3.2      | 12.5, 2.1, 3.4     |
| 3       | 11.7, 3.1, 5.8      | 10.2, 3.6, 6.1     |
| 4       | 12.7, 4.2, 3.3      | 11.3, 4.5, 2.1     |
| 5       | 12.2, 2.1, 2.6      | 10.4, 2.4, 3.7     |
| 6       | 12.7, 5.9, 1.1      | 10.8, 4.1, 5.4     |
| 7       | 10.1, 1, 1.2        | 10.1, 1, 1.9       |
| 8       | 12.5, 1.5, 4.6      | 11.8, 1.9, 5.9     |
| 9       | 12.2, 2.1, 2.6      | 10.3, 3.4, 2.7     |
| 10      | 12.7, 4.4, 4.8      | 12.7, 4.4, 4.8     |
| 11      | 11.5, 4.7, 6.3      | 11.6, 1.5, 6.4     |
| 12      | 10.1, 1.9, 4.9      | 11.5, 4.7, 6.3     |

*Stereotactic coordinates are actual postoperative lead locations confirmed by fusion of preoperative and postoperative images in relation to midcommissural point.

Table 3

Programming parameters before and after ILS.

| Right STN | Settings before ILS | Last ILS settings | A/C | A/PW/F | A/C | A/PW/F |
|-----------|---------------------|-------------------|-----|--------|-----|--------|
| A/C       | A/PW/F              |                   |     |        |     |        |
| 1         | C+0–1–              | 2.7/60/130        | ILS1: C+1– | ILS1: 3.0/60/125; ILS2: 2.7/60/125 |
| 2         | C+3–                | 4/60/130          | ILS1: C+2– | ILS1: 3.0/60/125; ILS2: 4.0/60/125 |
| 3         | C+1–                | 1.2/60/130        | C+1– | 2.7/60/125 |
| 4         | C+1–                | 2.5/60/140        | C+1– | 2.5/60/125 |
| 5         | C+2–3–              | 2.5/60/130        | C+2–3– | 2.5/60/125 |
| 6         | C+1–                | 2.4/60/130        | C+1– | 2.7/60/115 |
| 7         | C+1–                | 2.2/60/140        | C+1– | 1.9/60/125 |
| 8         | C+1–                | 1.2/60/160        | C+1– | 1.3/60/125 |
| 9         | C+1–                | 3.4/60/130        | ILS1: C+0– | ILS1: 2.9/60/125; ILS2: 3.2/60/125 |
| 10        | C+2–                | 2.9/60/130        | ILS1: C+1– | ILS1: 3.1/60/125; ILS2: 2.5/60/125 |
| 11        | C+1–                | 2.5/60/130        | ILS1: 3.1/60/125; ILS2: 2.5/60/125 |
| 12        | 3+0–1–              | 2.7/60/180        | 3+0–1– | 3/60/125 |

| Left STN | Settings before ILS | Last ILS settings | A/C | A/PW/F |
|----------|---------------------|-------------------|-----|--------|
| A/C      | A/PW/F              |                   |     |        |
| 1         | C+9–10–             | 2.5/60/130        | ILS1: C+11– | ILS1: 3.0/60/125; ILS2: 2.5/60/125 |
| 2         | C+7–                | 2.6/60/130        | ILS1: C+9– | ILS1: 2.5/60/125; ILS2: 3.0/60/125 |
| 3         | 11+9–               | 3.9/60/130        | ILS1: C+8– | ILS1: 3.2/60/125; ILS2: 1.7/60/125 |
| 4         | 2.7/60/140          | 3.9/60/130        | ILS1: C+6– | ILS1: 2.05/60/115; ILS2: 2.85/60/115 |
| 5         | 2.9–                 | 2.7/60/130        | ILS1: C+9– | ILS1: 2.1/60/125; ILS2: 2.3/60/125 |
| 6         | 2.1/60/140          | 3.1/60/160        | ILS1: 8+10– | ILS2: C+11– |
| 7         | 1.95/60/125         | 3.1/60/160        | 8+10– | 2.1/60/125; ILS2: 2.3/60/125 |
| 8         | 2.7/60/130          | 2.7/60/130        | C+9– | 2.3/60/125 |
| 9         | 3.1/60/130          | 3.3/60/130        | C+9– | 3.0/60/125 |
| 10        | 2.4/60/130          | 2.4/60/130        | C+9– | 2.4/60/125; ILS2: 2.8/60/125 |
| 11        | 2.6/60/130          | 2.6/60/180        | 11+8–9– | 2.6/60/125 |

A/C = anode/cathode, A/PW/F = amplitude/pulse width/frequency, ILS = interleaving stimulation, STN = subthalamic nucleus.
3. Results

Twelve patients received ILS because of stimulation-induced side effects (dysarthria and choreoathetoid dyskinesias), gait disturbance, and incomplete control of parkinsonism after multiple conventional stimulation treatments. All of the patients received ILS in only 1 hemisphere. Appropriate lead location was confirmed with postoperative reconstruction images (Table 2). ILS was considered when side effects appeared or there was unsatisfactory control of PD despite multiple programming sessions. The programming parameters before and after ILS are presented in Table 3.

We divided the patients into 4 groups based on symptoms and side effects, with some patients belonging to >1 group: gait disturbance, 8 patients (patients 1, 3, 4, 6, 8, 9, 10, and 11); stimulation-induced dysarthria, 2 patients (patients 5 and 7); stimulation-induced choreoathetoid dyskinesias, 3 patients (patients 3, 8, and 12); and partial benefit in PD symptoms but side effects at higher amplitude, such as motor fluctuation, tremor, and rigidity, 4 patients (patients 2, 4, 9, and 10).

PD itself may cause gait disturbances such as festinating gait and imbalance (group 1). All other symptoms (groups 2–4) are induced by stimulation. While the coordinates of DBS generally appeared to be suitable in our 12 patients, imaging data revealed that some of the electrode leads were not precisely located within the ideal target range in the STN. The working contacts produce stimulation current that spreads to different parts of the STN and adjacent structures, which can induce different benefits and side effects.¹²

Patients benefited not only from satisfactory improvement in gait disturbance and PD symptoms but also from the alleviation of stimulation-induced dysarthria and choreoathetoid dyskinesias. UPDRS-motor scores decreased from 22.42 ± 6.04 to 16.42 ± 4.99 following ILS (P < 0.01) without inducing further adverse effects. Patient self-evaluation data and UPDRS-motor scores are listed in Table 4. The results indicate that all of the patients had satisfactory treatment with ILS according to self-evaluation and decreased UPDRS-motor scores. Although patient 7 had an increase from 2 to 3 on the rigidity score, which includes the score of 4 limbs before and after ILS, she did not feel worse with respect to rigidity. At the conclusion of the study, all patients involved were still receiving ILS.

4. Discussion

After treatment with ILS, patients for whom conventional DBS was insufficient showed satisfactory improvement in PD symptoms. In addition, stimulation-induced side effects were alleviated, with a mean improvement in UPDRS-motor scores of 26.9%.

Although DBS is widely used to treat PD patients and shows remarkable motor benefits, suboptimal control of PD symptoms and stimulation-induced side effects often occur. We consider the following factors to explain why patients are not satisfied with conventional stimulation: first, patient’s expectations and individual differences. DBS usually does not alleviate all of the symptoms of parkinsonism and thus does not meet all of the patients’ requirements. To address the individual variability between patients, effective programming parameters should be customized. The degree to which a patient is satisfied with the benefits or can endure the side effects differs between patients. The size and anatomical position of the STN also may differ between individuals. Second factor is unsatisfactory lead location. The STN is olive-shaped, making insertion of the lead into the ideal target difficult. The contacts on the electrode are usually located in the STN and its adjacent structures. Depending on its location, the electrical field induced by the contact may affect different anatomical regions in the STN and its adjacent structures, providing specific improvements in PD symptoms or inducing adverse effects. This impression may be the reason it is more difficult to improve PD symptoms while alleviating side effects by conventional programming. Another factor is disease progression. With the progression of PD, previous programming parameters may not remain suitable for a patient; parameters should be adjusted accordingly. DBS may have limited benefits in advanced PD.

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1. ILS = interleaving stimulation, PIGD = postural instability and gait disturbance, including arising from chair, posture, gait, postural stability, and hypokinesia, SA = segmental activity, including finger taps, hand movements, rapid alternating movements, and leg agility, SE = self-evaluation, UPDRS = Unified Parkinson Disease Rating Scale.

2. UPDRS-motor was performed when patients were off medications.
The most important feature of ILS is that 2 programming settings can be interleaved in an alternating fashion on the same lead, with each of the programs specifying the amplitude, pulse width, and electrode contact. This feature might allow for shaping of the individualized current fields to fall below the side effect threshold and prevent stimulation of nontargeted anatomical regions in the STN and its adjacent structures, thereby reducing side effects and preserving motor benefits.

Previous studies of ILS are limited to case reports and rarely involve analysis. ILS for DBS in the STN significantly improves PD symptoms and alleviates side effects. One patient experienced improved symptoms in both PD and essential tremor after receiving ILS via a contact located in the STN and another in the ventrolateral anterior thalamus. ILS is also used in patients with medication-refractory dys dystonia who are regarded as nonresponders to pallidal DBS, resulting in considerable improvement of dystonia with no side effects.

PD itself may cause gait disturbances such as festinating gait and imbalance. Treatment of gait disturbance often remains unsatisfactory. Eight of our patients who suffered from gait disturbance had a limited response to multiple conventional programming treatments, although they had satisfactory control of PD. We suppose that this result is because DBS tends to alleviate segmental PD symptoms such as rigidity and tremor rather than gait disturbance. Reports indicate that low frequency and stimulation of the substantia nigra pars reticulata may improve gait disturbance.

Dysarthria is associated with the left STN lead. ILS can reduce dysarthria without compromising motor benefits in patients with essential tremor. Studies report that selecting more medially located electrodes and using bipolar mode with ILS may improve dysarthria. Two patients treated using single or double monopolar settings complained of dysarthria despite improvement of PD symptoms. The use of bipolar settings and low frequency with conventional programming also failed to achieve the desired result. We confirmed that the side effect of dysarthria is induced by DBS through turning on and off the device. For the main program (ILS1), we chose contact sites that had the most effective control of parkinsonism with limited side effect. For the other program (ILS2), we used other contact sites and increased the amplitude and pulse width gradually as necessary to achieve maximum benefit below the threshold for dysarthria.

To alleviate stimulation-induced choreoathetoid dyskinesias in 3 of our patients, we decreased the stimulation intensity (decreased amplitude, pulse width, frequency, or switched to bipolar mode) with conventional programming; however, parkinsonism control was incomplete. We observed that an effective ILS strategy involved the use of 1 program with contacts inducing antidyskinetic function to improve PD symptoms and the other program using contacts to meet the maximal motor benefits and avoid dyskinesias, a result that is consistent with other reports.

Finally, 4 patients undergoing conventional DBS showed unsatisfactory improvement in PD, with persistent tremor and rigidity. Increasing the stimulation intensity of DBS resulted in unbearable side effects. ILS in these patients allowed for the use of 1 program with satisfactory contacts below the threshold of adverse effects for improving parkinsonism and the other program using contacts to meet maximal benefits without side effects. This is our strategy for treating patients who experience partial improvement in PD symptoms but with side effects on DBS treatment at higher amplitude.

We would like to propose that ILS might further improve PD symptoms in patients who have satisfactory outcomes with conventional DBS programming. For example, 1 patient treated with a single monopolar setting may have satisfactory improvement in PD symptoms without adverse effects; however, if a double monopolar setting in conventional programming is used, severe side effects might occur. ILS that uses 1 program with 1 contact to give satisfactory control of parkinsonism without side effects and the other program with additional contacts with low amplitude (often 1–1.5 V) to shape the current field below the threshold of side effects might achieve more satisfactory improvement in PD symptoms than conventional programming. This novel strategy might meet the needs of patients with high requirements in improving parkinsonism.

Studies suggest that ILS may decrease battery life. Compared to single monopolar stimulation, ILS uses more contacts and more programming settings (e.g., amplitude, pulse width). Thus, ILS may increase electricity consumption and the frequency of recharges needed.

We conclude that ILS can be used when conventional programming proves unsatisfactory. ILS continues to emerge as an effective and well-tolerated programming strategy for maximizing symptom control in PD while decreasing stimulation-induced adverse effects. We report our experience of 12 PD patients using ILS to reduce stimulation-induced side effects and preserve motor benefit after conventional programming has been proven ineffective or intolerable. However, we should realize that most DBS patients are routinely treated with conventional stimulation and that not all patients benefit from ILS. ILS is not recommended as the first choice of programming and is recommended only when patients have unsatisfactory control of PD symptoms or stimulation-induced side effects after multiple treatments using conventional programming. A return to conventional stimulation may be required if ILS induces new side effects or the needs of the patient change. Limited by the retrospective nature of our report and a small number of patients, further investigation of ILS is needed.

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