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Subthalamic Deep Brain Stimulation With a New Device in Parkinson's Disease: An Open-Label Trial

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Objective: We aimed to evaluate the safety and efficacy of subthalamic nucleus deep brain stimulation (STN-DBS) with a new stimulator (Beijing PINS Medical Co., Ltd, PNS 1101) in Parkinson's disease (PD).

Materials and Methods: Forty patients received a PINS device implantation in the subthalamic nucleus. The effects of stimulation on motor score, activities of daily living, good-quality on-time, and the levodopa-equivalent dose were analyzed for all 40 patients with PD treated with bilateral or unilateral STN-DBS. The scores were collected at baseline in two conditions (on/off medication) and at 3, 6, 9, 12, and 24 months of follow-up with stimulation in the absence or presence of medication. The patients were followed up for two years.

Results: At 3, 6, 9, 12, and 24 months of follow-up, our results showed a significant increase from baseline in both activities of daily living and motor scores ($p < 0.001$) and good-quality on-time ($p < 0.001$); the daily levodopa-equivalent dose decreased compared with baseline ($p < 0.01$). No patient died during the study, and none of the adverse effects were classified as severe. All of the adverse events were resolved or improved by the end of the study.

Conclusions: STN-DBS with the PINS device significantly improved the symptoms of PD when compared with baseline in this trial. This new device may be recommended for the treatment of patients with advanced PD; however, a randomized, double-blinding trial will be required.

Keywords: deep brain stimulation, Parkinson's disease, PINS device, subthalamic nucleus, trial

Conflicts of Interest: Jian-guo Zhang is a consultant for PINS Medical. The other authors reported no conflicts of interest. PINS Medical contributed to the collection, monitoring, and management of the data. However, the manuscript was solely written by the authors. The authors take full responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the recruitment of patients or performance of surgery and were members of the writing committee.

INTRODUCTION

Deep brain stimulation (DBS) has been a widely accepted treatment modality for advanced Parkinson's disease (PD). It has proven to be a powerful treatment for the cardinal motor symptoms of tremor, rigidity, and bradykinesia. The subthalamic nucleus (STN) and the internal part of the globus pallidus (GPi) are the standard targets of DBS for PD. The effectiveness of both targets has been confirmed in numerous studies (1–12). However, most of the investigators favored the STN over the GPi for PD (12) because of some of its advantages: the postoperative medication dosage decrease was more prominent; the stimulation voltage was lower, and thus, the life of the pulse generator was longer, and the cost of DBS was reduced (13,14); and STN-DBS showed a trend toward better motor improvement in the early postsurgical stage compared with GPi-DBS (15).

Through 2010, more than two decades since the first usage of DBS in 1987 (16), more than 75,000 DBS procedures had been performed worldwide (17). Although the safety and efficacy of a constant-current DBS device has recently been shown (18), few choices of DBS devices are available. We believe that the high out-of-pocket expense of implantable hardware might be the chief obstacle in DBS implantation in countries where healthcare systems are developing, such as China, which is the largest developing country with a population of 1.3 billion, and also is an aging society facing a large population of PD patients. By contrast, as we previously reported, only

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Huan-guang Liu and Yu Ma contributed equally to this work.

2082 patients received DBS treatment from 1998 to 2009 (19). Thus, a similar but much cheaper DBS device will be needed. In this study, we aimed to assess the safety and efficacy of a new stimulator (PINS device, PNS 1101, PINS Medical Co., Ltd, Beijing, China) by implanting it into the STN to treat advanced PD. The activities of daily living and motor scores and daily levodopa-equivalent dose were evaluated by a movement disorder neurologist. To assess the duration of good-quality on-time, we adopted the use of PD diaries, which are a gold standard in many pharmacologic trials and have been validated in patients with PD and used as a primary outcome variable in DBS studies (14,18,20,21). The duration of good-quality on-time was recorded over a five-day period of evaluation in the present trial.

MATERIALS AND METHODS

Participants and Study Design

This was a prospective study at two hospital centers specializing in movement disorders in Beijing, China. The inclusion criteria for candidates were as follows: 1) 30–75 years old; 2) idiopathic PD diagnosed according to the UK Parkinson's Disease Society Brain Bank criteria (22); 3) a disease duration of five years or more; 4) Hoehn–Yahr stage II or greater; 5) severe motor fluctuations with disabling off periods and dyskinesias during on phases; and 6) no dementia or psychiatric abnormalities. Additionally, an improvement in the unified Parkinson's disease rating scale (UPDRS) motor score (part III) of 30% or more when comparing the off-medication score with the best on-medication score was required at baseline. All of the patients underwent diary training on how to rate their motor function and quality: 1) how to define the conditions of off and on; 2) on with nonbothersome dyskinesia or with bothersome dyskinesia. The exclusion criteria were as follows: 1) previous resective brain surgery or a cardiac pacemaker; 2) moderately severe parkinsonism in the context of unstable pharmacologic treatment; 3) dementia as assessed by the Diagnostic and Statistical Manual of Mental Disorders criteria or severe cognitive disturbances; 4) severe psychiatric symptoms (in particular, hallucinations and depression); 5) bad general health; and 6) lack of compliance at follow-up. The study protocol was submitted and approved by the Chinese State Food and Drug Administration. Ethical committee approval was obtained from each participating center before patient enrollment, and informed consent was obtained for each patient.

All of the patients with PD were evaluated by a movement disorder neurologist using the UPDRS (23,24), part III (motor) and part II (activities of daily living). We defined on medication as roughly one hour after a patient took antiparkinsonian medication when both the clinician and the patient indicated that the medication dose was effective. The scores were collected at baseline in two conditions (on/off medication) and at 3, 6, 9, 12, and 24 months of follow-up with stimulation in the absence or presence of medication. Changes in the duration of on-time without dyskinesia or with nonbothersome dyskinesia were measured in the patient diaries. The levodopa-equivalent dose also was measured in each patient (6). Lastly, the time required for the PINS device implantation surgery was documented.

Device Description

This PINS DBS device (PNS 1101) is a single-channel device designed by Tsinghua University and manufactured by Beijing PINS Medical Co., Ltd., Beijing, China. The implantable parts of the stimulator include the implantable pulse generator (IPG), the extension and the lead, and the telemetry/programming parts include the controller and the personal digital assistant, as shown in Figure 1. The IPG is 47 mm × 52 mm × 11 mm in size and 35 g in weight. The expected lifespan is two to six years depending on usage and stimulation parameters. The lead's diameter is 1.3 mm, and it has four stimulating contacts made of Pt-Ir alloy. The length of each contact is 1.5 mm, and the space between contacts is 0.5 mm. This device shares the same basic principles and user interface with Medtronic products, and it has unique designs in terms of circuitry, structure, and software. It only allows unilateral DBS through one lead programmed with one pulse generator. The amplitude (0–10 V), pulse width (60–450 μs), and frequency (2–250 Hz) can be programmed.

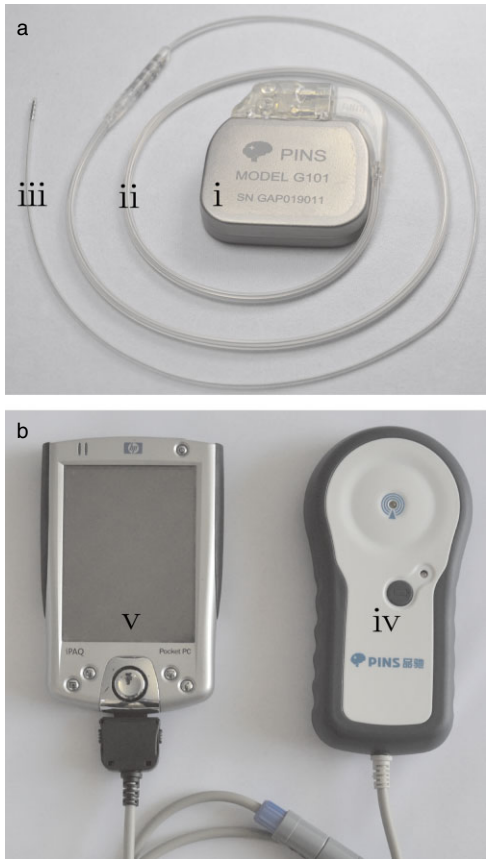

Figure 1. Photo of PINS device. a. implantable parts including (i) implantable pulse generator (IPG), (ii) extension, and (iii) lead; b. telemetry/programming parts including (iv) controller and (v) personal digital assistant (PDA).

Procedures

In the present trial, unilateral or bilateral implantations were performed in one surgery according to patient status. DBS devices (PNS 1101) were implanted using magnetic resonance imaging for targeting and microelectrode recording for target refinement, followed by intraoperative test stimulation of the DBS lead. The pulse generators were placed in the subclavicular position on the same day. A total of 75 DBS leads were implanted under local anesthesia, whereas the pulse generators were implanted under general anesthesia. Both of the participating centers used microelectrode recording to refine targeting and DBS placement and used head frames and physiology equipment. They were allowed to use existing DBS surgery equipment and were asked to physiologically refine

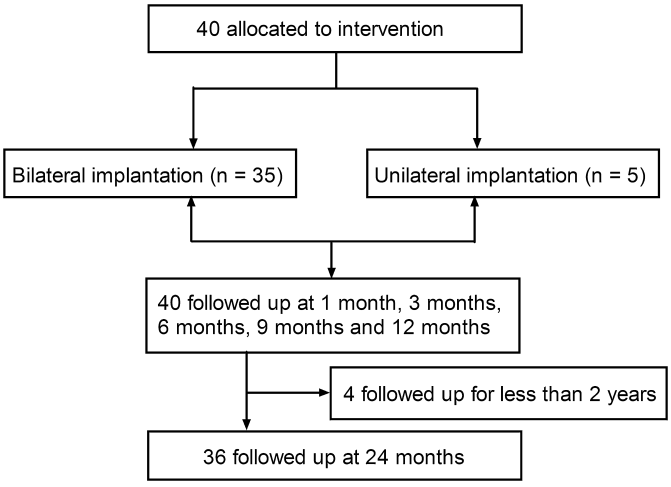

Figure 2. Trial profile.

the DBS targets based on their best medical practices. The devices were programmed one month after surgical implantation.

Table 1. Baseline Characteristics; Data Are *N* (%) or Mean (SD).

	Included patients (*N*=40)
Age (years)	56.32 (7.96)
Male	28 (70%)
Weight (kg)	63.81 (11.83)
Height (cm)	167.13 (9.24)
BMI	22.77 (3.16)
Onset age	46.35 (9.60)
Disease duration (years)	9.97 (4.37)
Main symptoms	
Tremor	35 (87.5%)
Rigidity	35 (87.5%)
Bradykinesia	32 (80%)
Gait dysfunction	23 (57.5%)
Drug-related complications	
Dyskinesia	18 (45%)
Wearing-off phenomenon	32 (80%)
Cramps	3 (7.50%)
Morning stiffness	22 (55.00%)
The "on–off" phenomenon	38 (95.00%)
Acute levodopa challenge test (UPDRS III)	
Off-medication	51.75 (14.76)
On-medication	20.73 (8.71)
Remission rate (%)	59.76 (14.62)
Mini-mental state examination	27.38 (1.71)

Statistical Analysis

The statistical analysis program SAS, release 9.13, was used for data analysis (SAS Institute Inc., Cary, NC, USA). Descriptive statistics are given parametrically as the mean (standard deviation). The global maximal level of significance was set at 5%. All p values are given for two-tailed tests. Differences in part II and part III of UPDRS, the on-time duration, and the levodopa-equivalent dose were statistically compared. The repeated measure was used to calculate the significance of the stimulation effect at 3, 6, 9, 12, and 24 months of follow-up. All statistical analyses were performed by a consultant statistician. A second statistician at an academic institution also performed and verified all statistical analyses and all of the tabular results reported for this study.

RESULTS

Between November 2009 and December 2011, 40 patients were assigned to intervention; 35 (87.5%) of 40 patients underwent bilateral implantations, and five patients (12.5%) underwent unilateral lead implantation. All of 40 patients completed one-year follow-up, and 36 patients completed two-year follow-up (Fig. 2). The patient baseline characteristics are presented in Table 1. Of the 40 patients with PD, three patients had previously undergone pallidotomy. The surgery time for implantation of the PINS DBS device (unilateral/bilateral leads plus extensions plus pulse generators) was defined as the time that elapsed between skin incision and skin closure. The median surgery time was 4.11 $\pm$ 1.29 hours. No patients died intraoperatively, and there were no surgical deaths through the study period. Each patient had postoperative CT scan in eight hours after surgery; there were no intracranial hemorrhages occurred.

Device failures were not reported during the study. Changes in device parameters occurred according to the standard operating procedures at each center. All parameters could be fine-tuned according to the patients' needs for symptom control. The stimulation parameter settings of amplitude, pulse width, and frequency did not change significantly during the study. Data for all of the 75 leads were available during the follow-up period. The stimulation parameters during the follow-up are summarized in Table 2. The effects of stimulation on motor score (UPDRS part III), the activities of daily living (UPDRS part II), good-quality on-time, and the levodopa-equivalent dose were analyzed for the patients with PD treated with bilateral or unilateral STN-DBS. In the present study, at 3, 6, 9, 12, and 24 months of follow-up, the activities of daily living and motor scores were significantly improved by stimulation ($p < 0.001$; Fig. 3a,b). A significant increase in good-quality on-time was observed compared with baseline ($p < 0.001$; Fig. 3c), and the daily levodopa-equivalent dose decreased compared with baseline ($p < 0.01$; Fig. 3d).

At 24 months, the endpoint of the follow-up, a significant mean improvement of 77.28% in the UPDRS part III (motor) was recorded when comparing the off-medication, on-stimulation condition with the baseline off-medication condition (12.61 [10.43] vs. 52.11 [14.26], respectively; $p < 0.001$). A significant improvement (mean = 76.54%) in the UPDRS part III also was observed in the on-medication, on-stimulation condition compared with the baseline on-medication condition (4.98 [7.45] vs. 22.18 [8.23], respectively; $p < 0.001$). The activities of daily living improved significantly (mean = 72.5%) in the off-medication, on-stimulation condition ($p < 0.001$) according to the UPDRS part II, from 20.66 (7.17) (baseline off-medication condition) to 5.1 (5.45). In the on-medication, on-stimulation condition, the activities of daily living also improved significantly (mean = 81.9%; $p < 0.001$), from 8.42 (4.87) (baseline on-medication condition) to 1.81 (3.96). Moreover, the daily requirement for Parkinson's disease medication (levodopa-equivalent dose) was reduced by 598.6 (896.4) mg at 24 months compared with baseline (1348.8 [1007.5] mg vs. 824.4 [545.0] mg, respectively; mean = 39.8%; $p = 0.003$). Good-quality

Table 2. Changes in the STN-DBS Parameters at 1, 3, 6, 9, 12, and 24 Months of Follow-Up.

Parameters	1 month	3 months	6 months	9 months	12 moths	24 moths
N	40	40	40	40	40	36
Amplitude						
Mean (SD)	2.0 (0.49)	2.2 (0.50)	2.3 (0.53)	2.5 (0.51)	2.6 (0.50)	2.7(0.47)
Range	1.0–3.2	0.6–3	0.6–3.3	0.5–3.5	1.2–3.7	1.5–3.7
Pulse width						
Mean (SD)	66.9(12.7)	71.1(14.6)	73.3(15.0)	77.5(14.9)	78.5(14.7)	78.5(14.7)
Range	60–90	60–90	60–90	60–90	60–90	60–90
Frequency						
Mean (SD)	142.8(12.5)	142.8(12.5)	148.6(14.2)	153.0(15.4)	154.8(16.5)	153.9(15.8)
Range	130–185	130–185	130–185	130–185	130–185	130–185

N, number of patients.

on-time improved by 12.6 hours per day (4.7 hours/day) at 24 months compared with baseline (4.44 [2.35] hours/day vs. 17.8 [4.6] hours/day; $p < 0.001$).

All 40 patients with an implanted PINS device were evaluated for adverse events during the two-year follow-up. No patient died during the study, and none of the adverse effects were classified as severe. Mental and psychiatric disturbances were usually transient, including anxiety, confusion, depression, and hallucinations, occurred in some patients. The other neurologic adverse effects related to the parameters were reported, such as dyskinesia, dysarthria, and paresthesia. They were resolved by regulating the parameters. No technical adverse events due to the PINS device were reported. Other unpleasant events, including falls, fatigue, and sleep disturbances, occurred with the progress of the disease in some patients, could be slight and resolved by readjusting the drugs and parameters.

DISCUSSION

This prospective, open-label clinical trial was conducted in patients who suffered from advanced PD. The results show that the PINS DBS device (PNS 1101) was relatively safe and efficacious. All of the 40 patients assigned to intervention received stimulation in the STN, bilaterally (35 patients) or unilaterally (five patients). They all have completed one-year follow-up, and 36 patients completed two-year follow-up. The clinical evaluations were based on the UPDRS, good-quality on-time, and levodopa-equivalent dose for PD. These variables were determined before surgery and 3, 6, 9, 12, and 24 months after DBS implantation.

In this study, the UPDRS part II and part III scores decreased more than 70%, and the levodopa-equivalent daily dose decreased by 39.8%. In addition, four patients (10%) were even not taking dopaminergic drugs at the 12-month follow-up. These benefits of STN-DBS with the PINS device paralleled other studies. In numerous previous reports (2,3,5,25–32), the fluctuating benefits observed after drug intake before STN-DBS were replaced by a stable improvement indicated by an increase of approximately 40–71% in motor symptoms. Medications have typically been reduced after STN-DBS; the mean postoperative reduction of the levodopa-equivalent daily dose has been reported at 30–67% (2,3,31,32). Patient quality of life improves after STN-DBS and is correlated with the improvement of motor symptoms (27,33–41). PD diaries were used in our trial, enabling the better estimation of the quantity and quality of effective on-time. Comparable with previous studies of DBS (14,18), STN-DBS with the PINS device improved the good-quality on-time by more than 10 hours per day at the 24-month follow-up.

The study design also focused on the safety of the new PINS stimulator. The adverse events reported in this study were not more severe than those reported in other published studies for either unilateral or bilateral surgical procedures (4,8,25,37,42–45). The major risks of DBS include hemorrhage, transient confusion, infection, and fracture, misplacement, or migration of the lead. The mean morbidity rate for DBS surgery is 3–4% (46). The target-related side effects of STN-DBS include dysarthria, neuropsychiatric problems (such as mood change, confusion, and apathy), eyelid-opening apraxia, weight gain, and stimulation-induced dyskinesia. Confusion, weight gain, and stimulation-induced dyskinesia tend to be limited to the first postoperative period (47). In this study, STN-DBS was associated with several adverse effects: neurologic adverse effects, such as dyskinesia, dysarthria, paresthesia, and mental and psychiatric disturbances including anxiety, confusion, depression, and hallucinations; other adverse events, such as falls, fatigue, and sleep disturbances. Device failure was not reported during the study. No intraoperative death or intracranial hemorrhage occurred in the present trial. However, the follow-up period of our study was shorter, and the sample size was smaller compared with other studies.

Parkinson's disease is thought to affect at least 100 persons in every 100,000. During the course of the disease, up to 50% of patients will have symptoms refractory to medication and will experience drug-induced dyskinesias (17). Many patients will seek surgical therapy and become DBS candidates. A randomized study has confirmed the superiority of STN-DBS in the medical management of PD at a six-month follow-up (27). Some studies have also shown that STN-DBS is a cost-effective treatment for advanced PD (48,49). Although these reports have proven that the overall cost of treatment for the life of the IPG (five–seven years) (50) is lower in implanted patients than in medically treated patients, the costs are due to the hardware that is needed at the time of implantation and replacement. New designs need to be cheaper to allow the management of advanced PD, and they also need to be available in countries where healthcare systems are developing (51). We believe that the high out-of-pocket expense of implantable hardware might be the chief obstacle in DBS implantation in these countries, including China, which is the largest developing country with a population of 1.3 billion, accounting for 20% of the total global population. Health outcomes in China have improved tremendously over the past decades. However, due to inadequate insurance coverage, high out-of-pocket payments, cost escalation, the inefficient use of scarce resources, and other problems (52), the performance of

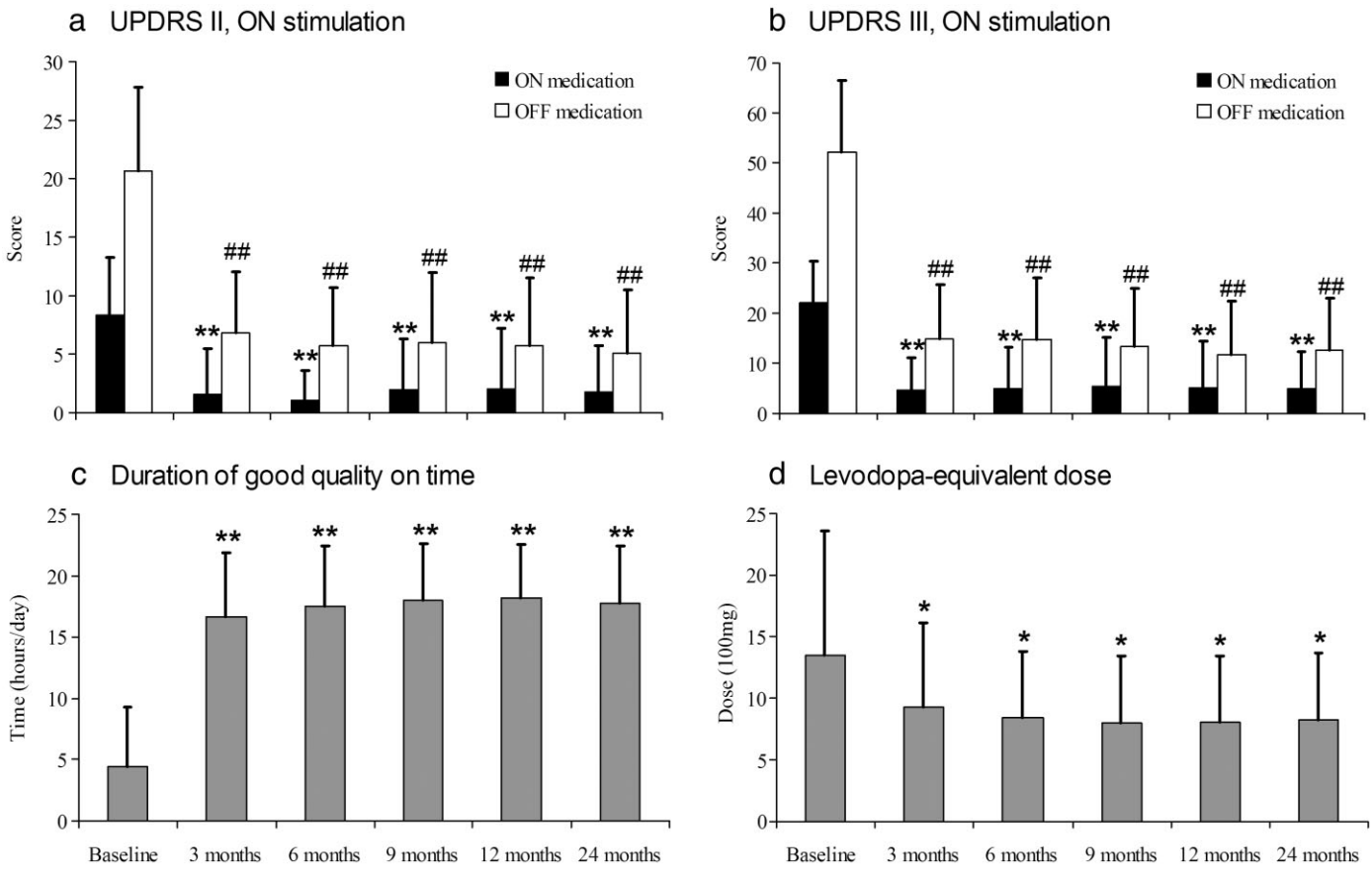

Figure 3. The effect of subthalamic nucleus stimulation: a. UPDRS II, on/off medication, on stimulation compared with baseline over the 24-month study (**$p < 0.001$ vs. baseline on medication; ##$p < 0.001$ vs. baseline off medication). b. UPDRS III, on/off medication, on stimulation compared with baseline over the 24-month study (**$p < 0.001$ vs. baseline on medication; ##$p < 0.001$ vs. baseline off medication). c. The duration of good-quality on-time compared with baseline over the 24-month study (**$p < 0.001$). d. The levodopa-equivalent dose compared with baseline over the 24-month study (*$p < 0.01$). The results are expressed as the mean (SD).

China's healthcare system cannot meet the people's demands, particularly for PD patients who require DBS therapy. A survey performed in 2003 showed that the urban and rural healthcare coverage only included 88% and 64% of those populations, respectively (53). Moreover, China also is an aging society facing a large population of PD patients. An epidemiologic survey indicated there were 1.7 million people aged 55 years or older suffering from PD in mainland China (54). Many will become drug resistant after five to seven years of intense levodopa usage and will require surgical intervention. By contrast, as we previously reported, only 2082 patients received DBS treatment from 1998 to 2009 (19). Thus, a similar but much cheaper DBS device will be needed. Taking into account of its efficacy and safety, if this stimulator has a much lower price, as expected (approximately $15,000 for bilateral stimulation) (19), more patients will be able to afford this treatment in the future.

It was an open-label trial without a random design, and it did not compare the PINS device with other devices. Further study and long-term follow-up are still required. However, it is encouraging that a prospective, multicenter, randomized, blind clinical trial of STN-DBS with a rechargeable dual-channel DBS system (PINS) is forthcoming and will enroll more than 53 patients with advanced PD.

CONCLUSION

STN-DBS with the PINS device (PNS 1101) for PD produced significant improvements in quality of life by improving motor function and good-quality on-time, and it also significantly reduced the daily PD drug requirement when compared with baseline. These improvements were maintained at two years after implantation. This new device may be recommended for the treatment of patients with advanced PD; however, a randomized, double-blinding trial will be required.

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Authorship Statement

The study was designed by Jian-guo Zhang, Yi Guo, and Yu Ma. The manuscript was prepared by Huan-guang Liu and Yu Ma. Data collection and analysis were performed by Huan-guang Liu, An-chao Yang, Wen-han Hu, Kai Zhang, Fan-gang Meng, Ming Ge, Tao Feng, Xin-hua Wan, Ren-zhi Wang, and Jin-zu Guo. All authors approved the final manuscript.

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COMMENTS

In this manuscript entitled "Subthalamic deep brain stimulation with a new device in Parkinson's disease: an open-label trial", the investigators evaluate the safety and efficacy of STN-DBS with a new stimulator (PINS device, PNS 1101). They implanted 40 patients with PD and state that at 3, 6, 9 and 12 months of follow up, there was a significant increase from baseline in both activities of daily living and motor scores ($p < 0.001$) and good-quality on-time ($p < 0.001$). Further, they find that the daily levodopa-equivalent dose decreased compared with baseline ($p < 0.01$). They conclude that the PINS device significantly improved the symptoms of PD and that the new device may be recommended for the treatment of patients with advanced PD. This is an important study as it provides an alternative to the high cost Medtronic device that is the only device available on the market. Clearly, a less costly alternative is welcomed given the increasing number of Parkinson's disease patients, the aging population in China, as well as the world. However, a few cautions need to be stated. First, this study has an important limitation of the fact that it is not a prospective randomized trial. Second, there was no direct comparison to the standard Medtronic device. Third, the study did not have a "on" stimulation versus "off" stimulation arm that would have helped to delineate the precise effect of the stimulation.

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Deep brain stimulation for all it's miraculous effects remains too expensive for the majority of the world's population. The two major current producers are very similar in their costs. Because of this unilateral lesions in Parkinson's disease becomes the realistic therapeutic option in many countries. At $15,000 for bilateral implants, this will have the possibility of altering decision making in many Asian countries. I wish the company all success.

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Comments not included in the Early View version of this paper.

