Research Article

Effects of bilateral subthalamic nucleus deep brain stimulation on motor symptoms in Parkinson's disease: a retrospective cohort study

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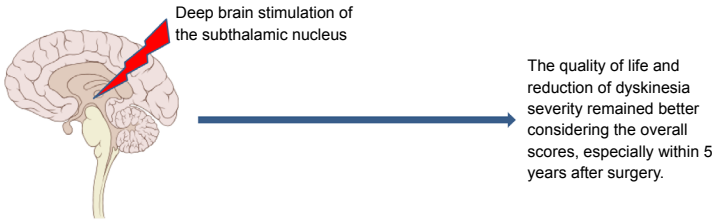
Guo-Xiong Cheng[1, #], Shu-Bin Yin[2, #], Ying-Hao Yang[1], Yuan-Hu Hu[2], Chih-Yang Huang[3, 4, 5, 6], Qian-Ming Yao[1, 2, *], Wei-Jen Ting[2, *]

Graphical Abstract *Bilateral deep brain stimulation of the subthalamic nucleus can effectively improve the motor effects in Parkinson's disease patients*



Abstract

Deep brain stimulation of the bilateral subthalamic nucleus (STN) is a therapeutic option for patients with Parkinson's disease (PD) in whom medical therapies have been ineffective. This retrospective cohort study analyzed the motor function of 27 patients with advanced PD, from the First Affiliated Hospital of Guangzhou Medical University, China, who received deep brain stimulation of the bilateral subthalamic nucleus and evaluated its therapeutic effects. The 10-year follow-up data of patients was analyzed in Qingyuan People's Hospital, Sixth Affiliated Hospital of Guangzhou Medical University, China. The follow-up data were divided into two categories based on patients during levodopa treatment (on-medication) and without levodopa treatment (off-medication). Compared with baseline, the motor function of on-medication PD patients improved after deep brain stimulation of the bilateral subthalamic nucleus. Even 2 years later, the motor function of off-medication PD patients had improved. On-medication PD patients exhibited better therapeutic effects over the 5 years than off-medication PD patients. On-medication patients' akinesia, speech, postural stability, gait, and cognitive function worsened only after 5 years. These results suggest that the motor function of patients with advanced PD benefitted from treatment with deep brain stimulation of the bilateral subthalamic nucleus over a period up to 5 years. The overall therapeutic effects were more pronounced when levodopa treatment was combined with deep brain stimulation of the bilateral subthalamic nucleus. This study was approved by Institutional Review Board of Qingyuan People's Hospital, The Sixth Affiliated Hospital of Guangzhou Medical University, China (approval No. QPH-IRB-A0140) on January 11, 2018.

Key Words: clinical trial; deep brain stimulation; dopamine; dyskinesia; levodopa; long-term follow-up; neurological function; Parkinson's disease; thalamus; UPDRS

Chinese Library Classification No. R454.1; R741; R338.2+4

Introduction

Parkinson's disease (PD), a neurodegenerative condition characterized by motor dysfunction, causes behavioral, cognitive and psychiatric deficits in the affected patients (Peng and Zhao, 2016; Elvsåshagen et al., 2020; Qu et al., 2020; van de Weijer et al., 2020). Dysfunctions in the motor circuit that controls movements, the associative circuit that controls executive functions and the limbic circuit that controls emotions and motivation, contribute to the symptoms in PD patients (Rommelfanger and Wichmann, 2010; Goulding et al., 2020). The subthalamic nucleus (STN) is a structure in the basal ganglia involved in motor function and any modulation in the STN causes alteration in impulse control. Therefore, deep brain stimulation (DBS) of the STN in human patients has

[1]Deparment of Neurosurgery, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong Province, China; [2]Deparment of Neurosurgery, The Sixth Affiliated Hospital of Guangzhou Medical University, Qingyuan, Guangdong Province, China; [3]Graduate Institute of Basic Medical Science, China Medical University, Taichung, Taiwan, China; [4]Department of Health and Nutrition Biotechnology, Asia University, Taichung, Taiwan, China; [5]College of Medicine, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Tzu Chi University, Hualien, Taiwan, China; [6]Medical Research Center for Exosome and Mitochondria Related Diseases, China Medical University and Hospital, Taichung, Taiwan, China

***Correspondence to:** Qian-Ming Yao, PhD, yaoqianming@gzhmu.edu.cn; Wei-Jen Ting, PhD, tingweijen@gzhmu.edu.cn.

https://orcid.org/0000-0001-5712-3448 (Wei-Jen Ting)

#Both authors contributed equally to this work.

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been reviewed and shown to be an effective treatment choice in patients with advanced PD (Choi et al., 2019). Long-term studies on STN stimulation show a clear effect on the cardinal motor symptoms of the disease for a notable period, however, the symptoms and PD conditions then deteriorate further (Jiang et al., 2015; Peng et al., 2018).

The basal ganglia of the striatum are strongly modulated by the neuromodulator, dopamine (Rommelfanger and Wichmann, 2010). However, the poor responses of motor symptoms to dopaminergic treatment cause postural instability and gait difficulties leading to substantial disabilities and reduced quality of life. STN-DBS would be expected to have a notable impact on such symptoms. Not all the effects of STN-DBS are clear; however, meta-analysis of several long-term studies on bilateral DBS in the STN and the internal globus pallidus internus did indicate that the procedures have acute beneficial effects on postural instability and gait disorders (Mirza et al., 2017; Lin et al., 2019). Clinical decisions would be based on not only the possible considerable effects of STN-DBS but also on the expectation that PD symptoms will eventually progress in a similar manner observed in non-operated patients with PD.

Conditions such as the dopamine dysregulation syndrome associated with dopaminergic treatment may also complicate long term therapies for PD and addiction remains a concern (De la Casa-Fages and Grandas, 2011; Napier et al., 2020; Olanow et al., 2020). It remains unclear whether stimulation in the STN is different in "off" medication and "on" medication patients in the long-term. This study evaluated the long-term efficacy of bilateral STN-DBS on PD symptoms and motor symptoms by performing a 10-year follow-up analysis of patients with advanced PD who underwent bilateral STN-DBS treatment at the First Affiliated Hospital of Guangzhou Medical University, China.

Subjects and Methods

Subjects

A retrospective cohort study was performed on 50 patients (21 males and 29 females aged 38 to 75 years, mean age 55.7 years) with PD undergoing STN electrode placement surgery. The course of the disease to surgery in the patients was about 4–15 years with an average duration of 9.8 years. Among the 50 patients, 27 were selected according to the following criteria (**Figure 1**): (1) patients with primary PD syndrome including classic motor signs of tremor, bradykinesia and rigidity and (2) patients with serious side effects such as exercise fluctuations or dyskinesia after taking medication. Of the patients studied, none were above 75 years of age and none presented with any clear contraindications to surgery, such as dementia or severe chronic disease. The specific details of patients included for the study are provided in **Table 1**. Ethical approval for this study was received from the Institutional Review Board of Qingyuan People's Hospital, The Sixth Affiliated Hospital of Guangzhou Medical University, China (No. QPH-IRB-A0140) on January 11, 2018 (**Additional File 1**).

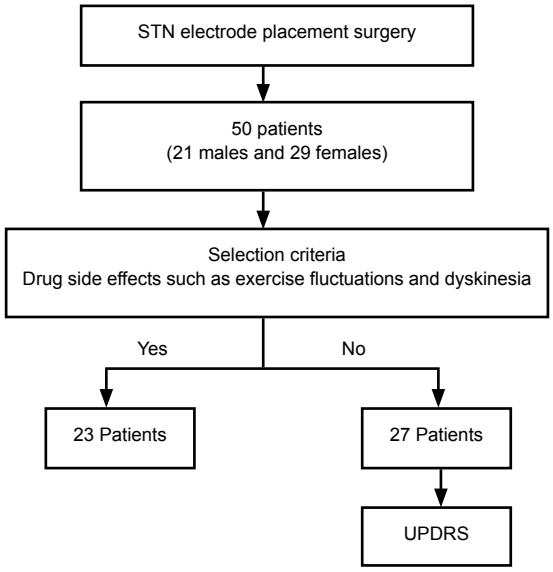

Figure 1 | **Flow chart of the study.**
STN: Subthalamic nucleus; UPDRS: Unified Parkinson's Disease Rating Scale.

Treatments

The patients received surgery at the First Affiliated Hospital of Guangzhou Medical University, China and data was analyzed at the Sixth Affiliated Hospital of Guangzhou Medical University, China. The selection of the deepest contact target in the STN was performed by MRI scan using the commercially available planning software Framelink (Medtronic, Minneapolis, MN, USA). Framelink 2.0 reformatted the MR image to the AC–PC plane to yield the calculated coordinates for the STN target (coordinates: 11–13 mm lateral, 4–6 mm below the AC-PC line and 1–3 mm inferior to the midcommissural point). Surgery was performed with local anesthesia and in off-medication condition. The DBS was implanted in two stages; first the DBS leads were implanted under local anesthesia and then the pulse generators (Active PC; Medtronic, Minneapolis, MN, USA) were implanted under general anesthesia. Microelectrode (Medtronic) recording was used to guide the STN placement. The four contacts of the stimulating electrode (Model 3389; Medtronic) were placed in the STN depending on the length of the STN thereby to maximize the area of stimulation.

The pulse generator was turned on after 3–4 weeks and regular follow-ups were made, at which the position of the electrode was checked with MRI. Parameters for optimal stimulation was set according to the observed clinical response to stimulation during the initial postoperative weeks; further adjustments on the parameters were made

Table 1 | **Distribution of Parkinson's disease patients with bilateral subthalamic nucleus deep brain stimulation details based on assessment time points**

	Before	3 mon	6 mon	12 mon	24 mon	36–60 mon	60–120 mon
n	27	10	10	13	12	5	4
Sex							
Male	17(63)	7(70)	7(70)	8(62)	7(58)	3(60)	3(75)
Female	10(37)	3(30)	3(30)	5(38)	5(42)	2(40)	1(25)
Surgery age (yr)	57.2±9.7	59.5±10.0	59.4±9.9	57.7±10.8	58.5±10.4	68.0±10.1	58.0±14.1
Tobacco use	1	0	0	1	0	0	0
Alcohol use	1	1	1	1	1	1	1
Hypertension	1	2	0	2	2	0	1
Cardiovascular disease	1	0	0	1	0	0	0
Diabetic mellitus	1	1	0	1	1	0	0

Data on sex are expressed as number (percent), data on surgery age are expressed as the mean ± SD, and other data are expressed as numbers.

as required in the follow-up visits. To confirm the optimal stimulation parameters, each patient underwent off- & on-medication assessments. The patients were followed up on recommendation for more than 24 months (after 3, 6, 12 and 24 months) and were assessed by multiple physicians based on the Unified Parkinson's Disease Rating Scale (UPDRS) score. The conditions of PD patients can be evaluated using the UPDRS, which comprises 42 criteria grouped in different sections. Section I (UPDRS I) represents mentation, mood and behavior; Section II (UPDRS II) includes assessment parameters for activities of daily living; Section III (UPDRS III) details motor functions and Section IV (UPDRS IV) represents complications (Kronenbuerger et al., 2015). The UPDRS scores were also recorded by tracking the patients during their visits to the hospital for other causes over 3–5 years and 5–10 years.

Statistical analysis

Groups (preoperative (n = 27), after 3 months (n = 10), 6 months (n = 10), 12 months (n = 13), 24 months (n = 12), between 3–5 years (n = 5) and 5–10 years (n = 4)) were compared using one-way analysis of variance followed by *post-hoc* Neuman-Keuls test using GraphPad Prism 5 (GraphPad Software, San Diego, CA, USA) software. P values of less than 0.05 indicate statistically significant differences. Data are expressed as the mean ± standard deviation (SD).

Results

Off-medication UPDRS I scores in PD patients with bilateral STN-DBS

There were no significant variations in the mentation, behavior and mood rating scales during the postoperative follow-up. However, 5–10 years of postoperative follow-ups showed a gradual increase in the UPDRS I score, which reflects developing intellectual impairment (**Figure 2**).

UPDRS III motor scores in PD patients with bilateral STN-DBS

At off-medication, there was a significant improvement in the UPDRS III motor scores observed at the 3-, 6-, 12- and 24-month and 3–5 year postoperative follow-ups compared with the preoperative motor score. At the 3-, 6-, 12- and 24-month and 3–5-year postoperative follow-ups, there were 40.2%, 54.4%, 57%, 40.6% and 40.8% improvements in walking, respectively, which equates to an improvement from weak slow walking with freezing to obvious improvement with mild difficulty (**Figure 3A**). There was no significant change in the rate of improvement in tremor and rigidity between postoperative 1-year and 5-year follow-ups. However, there was a notable sluggishness in action and speech together with noticeable stooped posture and walking stiffness at the 2-year follow up, as reflected in the respective UPDRS III scores (**Figure 3A**). On-medication patients scored lower UPDRS than off-medication. After DBS on-medication patients showed 25–30% improvement within 5 years compared with preoperative condition (**Figure 3B**). The UPDRS III scores in patients off- and on-medication deteriorated after 5 years.

Dosage of postoperative levodopa drug administration in PD patients with bilateral STN-DBS

Analysis of data from clinicians revealed that the average daily dose of levodopa was 953.2 mg, which was reduced after DBS to 569.76 mg and 570.76 mg at the 3- and 6-month follow-ups, respectively, which is almost a 40% reduction (P < 0.01 and P < 0.001). In the 12-month postoperative follow-up, the dosage was reduced by almost 53% to 450.63 mg (P < 0.001). However, the dosage had to be increased after 2 years postoperation.

Surgical complications in PD patients with bilateral STN-DBS

There was no worrying difference in the UPDRS IV scores to reflect any complications of therapy (**Figure 4**). Postoperative surgical complication arose in one case with electrode rejection. The electrode was removed 6 months postoperatively so no further response was observed. One case of pleural effusions was observed and thoracentesis conservative treatment was provided. No case of hemorrhage or death occurred.

Discussion

PD is a common and progressive neurodegenerative disease that is assessed based on clinical symptoms such as resting tremor, limb stiffness and movement retardation (Lewis and

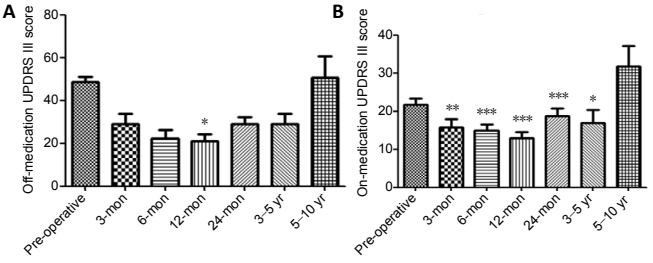

Figure 3 | **Off-medication (A) and on-medication (B) UPDRS III scores of Parkinson's disease patients with bilateral subthalamic nucleus deep brain stimulation.**

UPDRS III scores detail motor functions. Increasing scores represent the severity and longitudinal course of Parkinson's disease progression. Data are expressed as the mean ± SD and were analyzed using one-way analysis of variance followed by *post hoc* Neuman-Keuls test. Preoperative (n = 27) and 3-month (n = 10), 6-month (n = 10), 12-month (n = 13), 24-month (n = 12), 3–5-year (n = 5), and 5–10-year (n = 4) postoperative numbers are different. *P < 0.05, **P < 0.01, ***P < 0.001, *vs.* preoperative. UPDRS: Unified Parkinson's Disease Rating Scale.

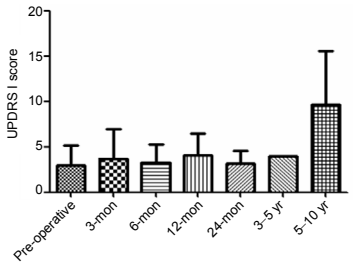

Figure 2 | **UPDRS I scores of Parkinson's disease patients with postoperative bilateral subthalamic nucleus deep brain stimulation.**

UPDRS I scores represent mentation, mood and behavior. Increasing scores represent severity and longitudinal course of Parkinson's disease progression. Data are expressed as the mean ± SD and were analyzed using one-way analysis of variance followed by *post-hoc* Neuman-Keuls test. Preoperative (n = 27) and 3-month (n = 10), 6-month (n = 10), 12-month (n = 13), 24-month (n = 12), 3–5-year (n = 5), 5–10-year (n = 4) postoperative numbers are different. UPDRS: Unified Parkinson's Disease Rating Scale.

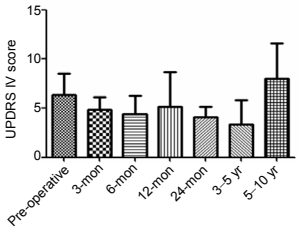

Figure 4 | **Postoperative UPDRS IV scores of Parkinson's disease patients with bilateral subthalamic nucleus deep brain stimulation.**

UPDRS IV scores represent complications. Increasing scores represent severity and longitudinal course of Parkinson's disease progression. Data are expressed as the mean ± SD and were analyzed using one-way analysis of variance followed by *post hoc* Neuman-Keuls test. Preoperative (n = 27) and 3-month (n = 10), 6-month (n = 10), 12-month (n = 13), 24-month (n = 12), 3–5-year (n = 5), and 5–10-year (n = 4) postoperative numbers are different. UPDRS: Unified Parkinson's Disease Rating Scale.

Liddle, 2012; DeMaagd and Philip, 2015). Since the 1960s, levodopa replacement therapy has been the most effective treatment for PD (Hornykiewicz, 2010). Although levodopa can significantly reduce the symptoms of patients in the initial treatment regime, long-term use will lead to conditions such as motor fluctuations and can also cause other diseases.

DBS has emerged as an effective procedure in the treatment of PD. In DBS, an electrode is implanted in the selected target region of the brain and a pulse generator generates a weak pulse of specific frequency such that the target is subjected to chronic stimulation to achieve the therapeutic purpose (Fox et al., 2011). Various randomized control studies have shown that DBS at STN and globus pallidus interna is superior to medication for PD in treating cardinal symptoms and motor complications (Rizzone et al., 2014; Anderson et al., 2017). Various reports have also shown that STN-DBS improves posture, gait and balance control. In this study, DBS surgery has been shown to lessen PD symptoms such as tremors, stiffness, slowness of movement and postural disorders and to show benefits in patients that have a poor response to drugs. DBS has been demonstrated to be more efficient than drug therapy in improving 'on' time UPDRS without causing dyskinesias, improve motor function by 35% better than medical therapy and enhance the quality of life 6 months postoperatively.

The early stage patients included in this study had closely comparable severity of PD and there was little difference in their onset age (mean 50 years). However, after DBS they exhibited a wide difference in their disease course; the significant difference in symptom scores demonstrates an effective outcome. Preoperative adjustments to drug treatment were made to obtain the best condition to assess the effects after surgery. Depression or anxiety associated with the operation received appropriate drug treatment.

In our study, bilateral STN-DBS surgery in PD patients in the off-medication state gave improvements in motor functions as observed through postoperative long-term follow-ups. Bilateral STN-DBS caused improvement in the motor symptom scores in PD patients during the off-medication state even after 2 years.

The UPDRS III scores reflected postoperative improvement of tremor and stiffness, which continued even up to 3–5 years with no noticeable deterioration. According to Guridi et al. (Guridi et al., 2012), STN stimulation induces a significant relief from PD symptoms in off-medication patients even after 3–5 years of surgery. In the present study, the UPDRS score showed a greater improvement for patients on medication than for those off medication in the first 5 years after the surgery compared with preoperatively. Further comparisons show that there was a similar trend in the changes in the off-medication and on-medication scores in all the respective follow ups. Although there was deterioration, the rate of deterioration at the 5–10-year postoperative follow up was similar in those with medication and in those without medication. The overall PD symptoms were less severe in patients on medication.

Even though slowness of movement was improved after STN-DBS, this effect did not last for long. Most off-medication patients were able to care for themselves until 5 years after surgery. However, patients 5–10 years post operation showed symptoms like tremor and stiffness worsening compared with cases observed during the follow-up up to 5 years. The overall UPDRS III score deteriorated significantly, suggesting no long-term benefit from DBS in off-medicated status.

Preoperatively PD patients during on-medication status have lower UPDRS scores than when off-medication and these were lowered further post surgery. However, there was little difference in their scores during the first 2 years post-surgery. At the 5–10-year follow-ups the UPDRS scores of patients on-medication began to show significant deterioration, mainly in terms of retardation, language, postural disorders, and stiffness. DBS surgery resulted in the largest percentage improvement in UPDRS scores of patients off-medication. According to the patients' own comparison, the patients' "off" state steadily improved during the 2-year postoperative follow-up period. However, the course of PD then accelerated and it was difficult to maintain a good state using DBS alone. In the first 2 years after surgery, the drug on time was significantly prolonged and the equivalent dose of levodopa significantly decreased with DBS. However, after 5 years, patients required a gradual increase in the dose of levodopa.

The deterioration in the effects of DBS in the long term has been attributed to brain histological changes resulting from electrode implantation – axonal alterations and concomitant disease – among other reasons. Astrogliosis and chronic inflammation are the common responses to DBS reported in various histological analyses. This also results in damage to neurons in the insertion site and can transmit excitation in the efferent axons. Axonal alterations and axonal swelling are also reported to result from chronic stimulation (Kronenbuerger et al., 2015). Lymphocytic infiltration, cerebellar axonal spheroids and Purkinje cell loss have also been observed in long term studies on DBS patients (DiLorenzo et al., 2010). These factors could potentially counter the continuing effects of DBS in the long term.

Our results indicate that STN-DBS did not improve PD symptoms in the long run, however, it provides the most benefits during the on-medication state when used in synergy with levodopa medication. The progression of PD increased, as seen in the later follow-ups. As seen from the UPDRS III, improvements from dyskinesia severity after STN-DBS surgery were clear, even at the postoperative follow-up after 5 years. The effects depended on the management of postoperative levodopa drug dosage. Postoperative stimulation parameters are generally more stable after the 1st year and did not increase much afterwards.

It is reported that STN-DBS results in improved motor symptoms of PD but also can show adverse effects on the cognitive function (Hershey et al., 2008; David et al., 2020). Despite a general perception and observation on the effect of STN-DBS on performance, findings are diverse and vary among individuals and studies. The variability of effects could be attributed to the asymmetry of the disease and variation in the precise location of the electrode and the field of delivery (Hershey et al., 2008). Therefore, further studies should be conducted to understand the effects of STN-DBS on motor functions and whether these effects can override the side effects of STN-DBS.

We have also identified two limitations in this investigation, which were due to the nature of the study and were seen in other similar studies. The sample size in this retrospective study varied because of some discontinuations at follow-up; therefore, the repeated measures of analysis of variance, which would otherwise be appropriate for such analysis could not be performed. Moreover, the UPDRS IV did not address the correlations of results with specific surgery related complications and target-related complications.

In conclusion, this study shows evidence, based on long term follow-ups, that bilateral STN-DBS can effectively improve motor function in PD patients. It maintained better quality of life and reduction of dyskinesia severity considering the overall scores, especially within 5 years after surgery. In the future, further analyses with more cases and with improved DBS technologies should improve the timing of treatment and stimulation techniques for the treatment of PD.

Author contributions: *Study design and manuscript revision: WJT, CYH,*

QMY; study implementation, data interpretion and manuscript draft: GXC, SBY; data analysis and manuscript revision: YHY, YHH. All authors approved the final version of the manuscript.

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Institutional review board statement: *This study was approved by the Institutional Review Board of Qingyuan People's Hospital, The Sixth Affiliated Hospital of Guangzhou Medical University, China (No. QPH-IRB-A0140) on January 11, 2018.*

Declaration of patient consent: *The authors certify that they have obtained the consent forms from patients or their legal guardians. In the form, patients or their legal guardians have given their consent for the patients' images and other clinical information to be reported in the journal. The patients or their legal guardians understand that patients' names and initials will not be published.*

Reporting statement: *The writing and editing of the article were performed in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) Statement.*

Biostatistics statement: *The statistical methods of this study were reviewed by the epidemiologist of The First Affiliated Hospital of Guangzhou Medical University, China.*

Data sharing statement: *Datasets analyzed during the current study are available from the corresponding author on reasonable request.*

Plagiarism check: *Checked twice by iThenticate.*

Peer review: *Externally peer reviewed.*

Open peer reviewers: *Francisco Capani, Universidad Argentina John F Kennedy, Argentina; Colin J. Barnstable, Penn State Hershey Eye Center, USA.*

Additional files:

Additional file 1: *Hospital Ethics Approval (Chinese).*

Additional file 2: *Open peer review reports 1 and 2.*

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