Safety and feasibility of curved lead simultaneously implanted into pedunculopontine nucleus and subthalamic nucleus

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To the Editor: Combined nuclei stimulation may have a synergistic effect on controlling the symptoms of nervous system diseases and improving quality of life.[1] However, increasing of leads may increase costs and complications.[2] Therefore, our study aims to investigate the safety and feasibility of the single curved lead, which can simultaneously reach both subthalamic nucleus (STN) and pedunculopontine nucleus (PPN).

The animal experiment, which was ethically approved ([No. 2019] [234]) by the animal research ethical committee of the Second Affiliated Hospital of Fujian Medical University, was performed complied with the Animal Research: Reporting of In Vivo Experiments (ARRIVE) guideline. Twenty healthy adult male Sprague-Dawley rats weighing 290–310 g were randomly and equably assigned to four groups: (1) Sham-modeled group (Group A): all rats were injected with 3 μL of 0.9% saline containing ascorbic acid (0.2 mg/mL) into the right medial forebrain bundle (MFB); (2) Sham-operated group (Group B): all rats were injected with 3 μL 6-hydroxydopamine (6-OHDA) (3.5 μg/μL) into the right MFB without lead implantation; (3) Curved lead group (Group C): all rats were injected with 6-OHDA into the right MFB and then implanted a curved lead (titanium wires) into right STN and PPN; (4) Straight lead group (Group D): all rats were injected with 6-OHDA into the right MFB and then implanted two straight leads (titanium wires) into right STN and PPN. Leads were implanted into the right STN (from bregma: 3.6 mm posterior, 2.5 mm lateral, and 8.0 mm ventral) and the right PPN (from bregma: 7.0 mm posterior, 2.0 mm lateral, and 8.0 mm ventral) for all rats in groups C and D. Schematic illustrations of the implantation pathway in rat brain of the curved lead and straight lead are shown in Figures 1A and 1D, respectively.

Surgical preparations and perioperative care for lead implantation surgery were routinely performed in the same way as stereotaxic surgery. Fifteen minutes prior to surgery, all rats were anesthetized by intraperitoneal injection of sodium pentobarbital (40 mg/kg). After anesthesia, the rats were fixed on a stereotaxic apparatus (RWD stereotaxic frame 68511, RWD Life Science Co., Ltd, Shenzhen, Guangdong, China). The implanted leads were fixed onto the skull by dental cement. Curved and straight titanium wires with the diameter of 0.4 mm (BaoTi Group Ltd, Baoji, Shaanxi, China) were used in this study. For each rat in the straight lead group, one straight lead was implanted into the right STN and the other into the right PPN. The method of curved lead implantation, which was described in the Supplementary File, http://links.lww.com/CM9/B193, was different from the conventional method of straight lead implantation. After surgery, all rats were given buprenorphine (0.12 $g \cdot kg^{-1} \cdot d^{-1}$), penicillin (80 $g \cdot kg^{-1} \cdot d^{-1}$), and saline (10 $mL \cdot kg^{-1} \cdot d^{-1}$) by subcutaneous injection for two consecutive days, and each rat was given 15 g/d of feed with free access to water.

To examine the safety of curved lead, neurobehavioral scale score at 0.5, 1, 3, and 7 d after surgery, and Morris water maze (MWM) test (Zhenghua Biologic Apparatus Facilities Co Ltd, Huaibei, Anhui, China) were utilized to evaluate the cognitive and motor function of rats.[3,4] Also, Magnetic Resonance Imaging (MRI, Bruker, Germany) scan was used to evaluate obvious complications (intracranial hemorrhage, swelling) in the rats after lead implantation. After finishing all neurobehavioral

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Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000002398

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Chinese Medical Journal 2022;135(20)

Received: 18-08-2022; **Online:** 17-11-2022 **Edited by:** Peifang Wei and Xiangxiang Pan

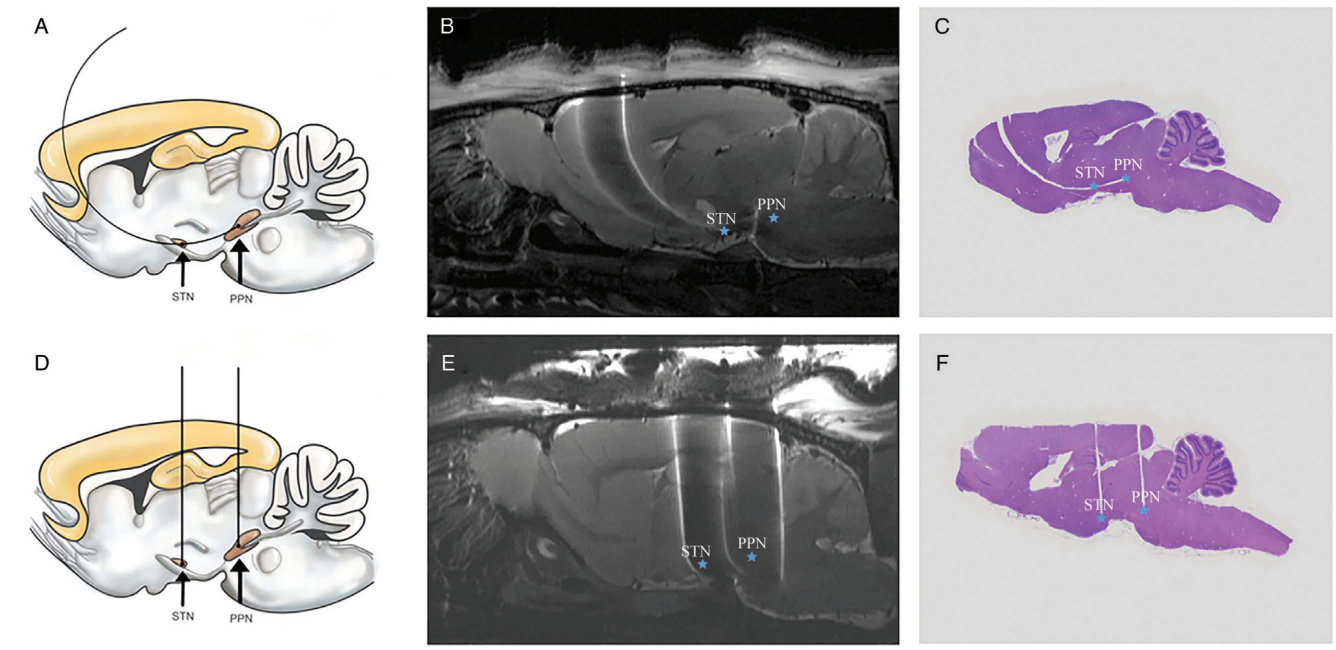

Figure 1: The lead placement under two pathways. (A) Schematic illustrations of the implantation pathway in rat brain with the curved lead. (B) Postoperative magnetic resonance imaging of the curved lead implantation. (C) Histological section (original magnification × 0.5) of rat brain implanted with a curved lead. (D) Schematic illustrations of the implantation pathway in rat brain with the straight leads. (E) Postoperative magnetic resonance imaging of the straight leads implantation. (F) Histological section (original magnification × 0.5) of rat brain implanted with two straight leads. PPN: Pedunculopontine nucleus; STN: Subthalamic nucleus.

tests, rats were deeply anesthetized with sodium pentobarbital, and transcardically perfused with saline followed by 4% paraformaldehyde solution. Sections of rat brains were obtained and stained with hematoxylin and eosin. We adopted two methods—MRI scan and histological sections, to evaluate the location of implanted lead. The lead position was evaluated by two investigators who were blind to the rats' behavioral results, based on MRI slices and histological sections.

The statistical analysis was performed by SPSS 26.0 (SPSS Inc., Chicago, IL, USA). The data following normal distribution were expressed as mean ± standard error of the mean. The comparison of neurobehavioral scores and data of the training trials of MWM test was performed by multivariate analysis of variance (MANOVA) of repeated measuring. Further comparison between groups was based on *post hoc* tests of multiple comparisons. The results of the probe trial of MWM test among four groups did not follow normal distribution, and were described as medians (25th and 75th percentiles) and compared by nonparametric test (Kruskal–Wallis H test). $P < 0.05$ was considered statistically significant.

There were no obvious complications (intracranial hemorrhage, swelling) in the rats after lead implantation. For "curved lead pathway", the curved lead tip was located in the PPN after passing through STN [Figures 1B and 1C]. For "straight lead pathway", the lead tip was located in the STN and PPN [Figures 1E and 1F]. Therefore, we confirmed that the curved leads and the straight leads were successfully implanted. The neurobehavioral scores at 0.5, 1, 3, and 7 d after surgery in sham-modeled group were statistically significantly lower than that of sham-operated group, curved lead group and straight lead group ($P = 0.002$, $P = 0.003$, and $P = 0.002$, respectively). There were no significant difference in neurobehavioral scores between the straight lead group and the curved lead group at 0.5, 1, 3, and 7 d after surgery. In the MWM test, the escape latencies were significantly different among the four groups ($F = 263.15$, $P < 0.001$). The escape latency of curved lead group was similar to the straight lead group ($P = 0.209$). In the probe trials, the sham-modeled group spent more time searching in the quadrant where the platform was previously located than the sham-operated group ($P = 0.041$), curved lead group ($P = 0.008$) and straight lead group ($P = 0.008$); the percent of time in four quadrants of the curved lead group was similar to that of the straight lead group (Target: 33.0% [32.0–34.0%] *vs.* 34.0% [32.5–34.0%], $Z = -0.565$, $P = 0.572$; Right: 22.0% [21.0–23.0%] *vs.* 22.0% [21.5–23.5%], $Z = -0.542$, $P = 0.588$; Opposite: 22.0% [21.0–22.5%] *vs.* 22.0% [22.0–23.0%], $Z = -1.247$, $P = 0.212$; Left: 23.0% [22.0–24.5%] *vs.* 22.0% [21.0–22.5%], $Z = -1.611$, $P = 0.107$).

Considering the lower treatment efficiency of single target stimulation, multi-target stimulation may be a promising direction for future studies. Compared to multiple straight leads, signal curved lead not only stimulates multiple targets simultaneously, but also has the advantages of inexpensiveness and convenience, indicating its application prospects in the field of brain function.

With the aid of the novel stereotaxic system and the automatic calculation algorithm for the "curved lead pathway",[5,6] we successfully implanted the curved lead to both STN and PPN in a rat model. The similar functional outcomes between curved lead group and straight lead group revealed that the curved lead passing through STN and located at PPN is feasible and safe.

There were some deficiencies in this study. First, computed tomography (CT) scan for complication evaluation was not performed in our study. Considering the artifacts caused by lead in MRI scans, further study is needed to perform postoperative consecutive CT scan to identify the intracranial hemorrhage and swelling after lead implantation. Second, we could not evaluate the stimulation function of the curved lead implanted in the target nuclei yet due to technology limitation, and our future research will focus on solving it.

Overall, our study confirmed that the curved lead could reach both STN and PPN with safety and efficacy.

Funding

This study was supported by the grant from National Natural Science Foundation of China (No. 81901395).

Conflicts of interest

None.

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How to cite this article: Wang W, Chen X, Chen D, Chen Y, Yu L, Lin Y, Kang D, Chen X, Ding C. Safety and feasibility of curved lead simultaneously implanted into pedunculopontine nucleus and subthalamic nucleus. Chin Med J 2022;135:2509–2511. doi: 10.1097/CM9.0000000000002398