Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.
## eTable 1  Primary and secondary outcomes

| Domain                | Instrument                                           |
|-----------------------|------------------------------------------------------|
| Anxiety state         | Hamilton Anxiety Scale\(^a\)                        |
| Mental Status         | Unified Parkinson’s Disease Rating I \(^b\)         |
| Emotional well-being  | 39-item Parkinson Disease Questionnaire - Emotional well-being\(^c\) |
| Clinical assessment   | Unified Parkinson’s Disease Rating \(^d\)           |
| Activities of daily living | 39-item Parkinson Disease Questionnaire - Activities of daily living\(^e\) |
| Quality of life       | 39-item Parkinson Disease Questionnaire\(^f\)        |
| Blood serum levels of ACTH | ELISA Kit of adrenocorticotropic hormone\(^g\) |
| Blood serum levels of CORT | ELISA Kit of cortisol\(^h\)                          |

\(^a\) Scores range from 0 to 56, with higher scores indicating more serious anxiety.
\(^b\) Scores range from 0 to 16, with higher scores indicating worse mental status.
\(^c\) Scores range from 0 to 28, with higher scores standing for worse emotional well-being.
\(^d\) Scores range from 0 to 192, with higher scores indicating more severe overall symptoms of Parkinson's disease.
\(^e\) Scores range from 0 to 20, with higher scores indicating worse activities of daily living.
\(^f\) Scores range from 0 to 156, with higher scores indicating worse quality of life.
\(^g\) Higher content indicates more activation of the HPA axis.
\(^h\) Higher content indicates more activation of the HPA axis.
eTable 2 Levodopa equivalent dose conversion

There are many kinds of anti Parkinson drugs. Patients often take multiple anti Parkinson drugs at the same time, so it is impossible to evaluate the baseline situation of patients before treatment. In this study, the calculation software of levodopa equivalent dose was used to convert different kinds of anti Parkinson drugs taken by patients into levodopa equivalent dose.

| Drug                        | Conversion |
|-----------------------------|------------|
| L-dopa                     | 1          |
| L-dopa CR                  | 0.75       |
| L-dopa + Entacapone         | 1.33       |
| L-dopa + Opicapone          | 1.7        |
| L-dopa + Tolcapone          | 1.5        |
| Rotigotine                  | 30         |
| Ropinirole                  | 20         |
| Pramipexole                 | 100        |
| Selegiline                  | 10         |
| Rasagiline                  | 100        |
| Apomorphine                 | 10         |

eTable 3 Operation rules of Real acupuncture

|                | Needle specification | Acupuncture angle     | Acupuncture depth |
|----------------|----------------------|-----------------------|------------------|
| Si Shen Zhen   | 0.25 × 25 mm         | 45 degree angle       | 15-20mm          |
| GV 24 (shen ting) | 0.25 × 25 mm       | 45 degree angle       | 15-20mm          |
| GV 29 (yin tang)| 0.25 × 25 mm         | 45 degree angle       | 15-20mm          |
| HT7(shen men)  | 0.25 × 25 mm         | 90 degree angle       | 15-20mm          |
| SP 6 (san yin -jiao) | 0.25 × 40 mm       | 90 degree angle       | 25-30mm          |
eFigure 1. The relationship between PD and PDA.
eFigure 2 Selection and location of the acupoints for acupuncture
eAppendix 1

The masking effect of sham acupuncture

1. Introduction

Acupuncture, one of the essential therapeutic methods of traditional Chinese Medicine, is used in many clinical practices in China and overseas. As the interest of acupuncture develop in the world, a great deal of acupuncture clinical studies were conducted. However, some systematic review showed that many acupuncture clinical trials are of low evidence-based for they are out of blinding[1-4]. Non-blinding gives rise to expected bias, and placebo effects[5] are inevitably existed which make trials less convincing. Thus, a practical placebo acupuncture appliance is urgent needed.

The first reported placebo acupuncture appliance[6], designed by Streitberger and Kleinhenz, was covered by a plastic sheet so that patients cannot see whether the needle was inserted or not. Nobuari Takakura and Hiroyoshi Yajima modified the placebo appliance with an opaque tube[7]. The two placebo appliances are still popular and used in many randomized trials[8-10] but they can just insert straight without changing the angle. Therefore, these appliances cannot fix different acupoints[11] such as Baihui (DU20), which stands on the head and needs inclined angle. Given the present defective placebo acupuncture appliances, designing a new practical placebo acupuncture appliance that matches different inserted angle is pressing.
2. A new practical placebo acupuncture appliance

To match acupuncture clinical study practically, our team designed a placebo acupuncture appliance, which can adjust different needling angles. The appliance has already granted the patent by China national intellectual property administration (No. ZL202121352221.7). The placebo acupuncture appliance contains a pedestal and a tube. The pedestal, made by resin material, is opaque so that it can isolate patients’ eyesight, and they cannot visually decide whether the needle is inserted into skin or not. There is a sticky patch in the base of the pedestal to ensure the pedestal can stick to the skin. The tube is transparent so that it is convenient for doctors to insert the needle through the tube. In addition, we designed two types of pedestals. One is hollowed in the base, the other is not hollowed. For the sake of real
acupuncture, we use the hollowed appliance, and the needle can insert into the skin directly and hygienically. For the sake of placebo acupuncture, we use the non-hollowed appliance and the blunt needle. The sticky base can clamp the non-invasive needle so that the needle will not drop whenever patients move. For different angles, there are three holes in the pedestal, one on the top and two on the sides. If putting the tube in the top hole, then the needle can hold a straight angle while putting the tube in the side hole, the needle is beveled to the skin that can match the need of needling in scalp (Figure 5).

![Needle at a 15 degree angle](image1.png)  ![Needle at a 90 degree angle](image2.png)

**eFigure. 3. placebo acupuncture appliance diagram**

![Different bases of the appliance](image3.png)

**eFigure. 4. different bases of the appliance**

![Placebo acupuncture on the head](image4.png)

**eFigure. 5. placebo acupuncture on the head**

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3. Protocol for masking effect of sham acupuncture

In order to testify the masking effect, we recruited 60 volunteers, aged 24 to 66, with no sign of disease, to test whether they can judge the type of acupuncture they received. All these volunteers have experience of acupuncture treatment and was told that they would test a new acupuncture appliance. This pilot study is approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou University of Chinese Medicine (No.K[2021]015).

The study was conducted by two experienced acupuncture therapists, graduated from Guangzhou University of Chinese Medicine and have clinical experience in the First Affiliated Hospital of Guangzhou University of Chinese Medicine over two years. Each volunteer with a patch over their eyes and was randomized received real or placebo acupuncture in scalp and limbs, radial and ulnar, such as Shenting (DU24), Hegu (LI4) and Chize (LU5) to simulate clinical scene in reality. After disinfection the acupoints, we stuck the pedestals to volunteers’ skin and chose sharp or blunt needles via guiding tube according to the allocation. We removed the needles 2 minutes later. Once the needles removed, we asked volunteers how they felt by visual analogue scale (VAS), testing the feeling of acupuncture, and which type of acupuncture did they believed they received.
4. Results

The outcome showed that there is no VAS score significant difference between real acupuncture group and placebo acupuncture group. The Cohen’s Kappa coefficient of two groups was -0.033(95% CI:0 to 0.28). No statistically significant difference either.

eTable 4 VAS scores [M (P25, P75)]

| VAS score | Real acupuncture group (n=30) | Placebo acupuncture group (n=30) | Z  | P    |
|-----------|-------------------------------|---------------------------------|----|------|
| score     | 4.50(2.00,7.75)               | 6.00(2.00,8.00)                 | -0.724 | 0.469 |

VAS scores of two groups did not conform to normal distribution (Shapiro-Wilk=0.903, 0.889, P=0.010, 0.005), so mann-Whitney U test was used for analysis, and data results were reported by median and quartile.

eTable 5 Cohen’s kappa of sham acupuncture

|                 | Believed received real acupuncture | Believed received placebo acupuncture | k   | P    | 95%CI |
|-----------------|-----------------------------------|--------------------------------------|-----|------|-------|
| Real acupuncture group (n=30) | 13(43.33%)                        | 17(56.67%)                           | 0.033 | 0.793 | 0.028 |
| Placebo acupuncture group (n=30) | 12(40.00%)                        | 18(60.00%)                           |     |      |       |
5. Discussion

Based on the result, we consider the new placebo acupuncture appliance has a good masking effect. On the one hand, volunteers felt the same no matter what type of acupuncture they received. But the pain volunteers felt fluctuates, we thought it is due to the different pain tolerant level of different people. On the other hand, consistency was evaluated as perfect if $\kappa > 0.8$, good if $0.6 < \kappa \leq 0.8$, moderate if $0.4 < \kappa \leq 0.6$, fair if $0.2 < \kappa \leq 0.4$, and poor if $\kappa \leq 0.2$[12]. The Cohen’s kappa less than 0.2 so that the consistency between the type of acupuncture volunteers received and the type they thought was quite poor. Thus, we can draw a conclusion that volunteers cannot distinguish what type of acupuncture they received. The new placebo appliance has a good masking effect.

CONSORT[13] statement and its extensive acupuncture statement, STRICTA, are used for evaluating the quality of randomized controlled trials (RCTs). Since the two statements has introduced in China, the quality of acupuncture RCTs improved[14]. Trials protocols can be modified according to the two statements, but the perceived difficulty of acupuncture RCTs is blinding. CONSORT and STRICTA statements mentioned blinding as one of the important items when evaluating RCTs. If blinding in acupuncture can be realized, the quality and evidence-based level of acupuncture RCTs will improve. The new placebo acupuncture appliance can switch different inserted angles to meet the need of acupoints in scalp. The pilot study showed that the appliance blinda patients practically and is simple to use. Any trained researchers can use it with
no difficulty. Given the good masking effect and simple usage, the new practical placebo acupuncture appliance can meet the requirements of acupuncture RCTs and improve the level of evidence. Considering that patients’ expectation has a great impact on treatment effect[15] and doctors’ expertise rather than reported bias influence acupuncture’s effectiveness[11], we focus on reduce the bias of expectation. The new placebo acupuncture appliance is practical in clinical trials[16], we will put our best foot forward to promoting it and help to improve the evidence-based level.

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