Wrist-ankle acupuncture and Fluoxetine in the treatment of post-stroke depression: a randomized controlled clinical trial

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Abstract

OBJECTIVE: To investigate the effects of WAA combined with fluoxetine in the clinical treatment of post-stroke depression (PSD).

METHODS: In this randomized, controlled and single-blind trial, 105 PSD patients who met the inclusion criteria were randomly divided into three equal groups: Thin wrist-ankle acupuncture (WAA) group (Thin WAA needle + Fluoxetine), Thick WAA group (Thick WAA needle + Fluoxetine), and Sham WAA group (sham WAA needle + Fluoxetine). In this trial, the primary outcome was Hamilton Depression Scale (HAMD), while the secondary outcomes included Zung self-rating depression scale (SDS) and World Health Organization Quality of Life BREF (QQL).

RESULTS: Ninety nine PSD patients completed all the treatment. The HAMD scores and SDS scores of all the three groups decreased after treatment ($P < 0.05$); thick WAA group and thin WAA group decreased more obviously than the sham WAA group ($P < 0.05$). There was no significant difference between the QQL scores of the three groups ($P > 0.05$). There was no significant difference in the scores of the three scales between the thick wrist ankle needles and the thin wrist ankle needles ($P > 0.05$).

CONCLUSION: The present study showed that WAA combined with fluoxetine can relieve the symptoms of depression after stroke. WAA therapy could improve the antidepressant effect of fluoxetine.

Keywords: Depression; Fluoxetine; Wrist-ankle acupuncture; Randomized controlled trial
INTRODUCTION

Depression occurs as the most common neuropsychiatric complication after stroke, and about 1/3 of stroke patients have shown different degrees of depressive symptoms. Post-stroke depression (PSD) not only affects the recovery of limb function because long time depression can lead to cognitive impairment and limb function deterioration, but is also related to the recurrence of stroke. Early antidepressant treatment can effectively prevent the occurrence of depression, and long-term antidepressant drugs have positive effects in relieving depression symptoms and recovering daily behavioral capacity and cognitive function. Antidepressant drugs commonly used in clinic includes psycho stimulant, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors and tricyclic antidepressants. Fluoxetine has currently become the first-line antidepressant drug as one kind of SSRIs. However, fluoxetine has some side effects, such as gastrointestinal reactions, headache, sexual dysfunction and insomnia etc. Acupuncture and moxibustion treatment, on the other hand, have been proved to be clinically effective. It not only improves the mental state of the patient while promoting functional rehabilitation, but also has few side effects. WAA is a typical kind of acupuncture, by which the needle is located only on the wrists and ankles. It is unnecessary to have “De Qi” which is a key factor for the therapeutic efficacy of traditional acupuncture. The operation of WAA therapy is simple, with which the patient can easily comply, and it has a good effect on pain and neuropsychiatric diseases.

This study aims to further verify the efficacy of WAA combined with fluoxetine in the treatment of PSD by observing whether it can enhance the efficacy and reduce the side effects of fluoxetine, and determining whether the diameter of the needles has any impact on the results.

METHODS

Participants and recruitment

The participants for this study were recruited from Traditional Chinese Medicine Acupuncture Department of Changhai Hospital who had completed the randomized and controlled trial “Wrist-ankle acupuncture (WAA) and Fluoxetine in the treatment of post-stroke depression” (Chinese Clinical Trial Registry, identifier: ChiCTR-IOR-15006313). Posters of this trial had been put on notice boards to recruit potential participants in the hospital. The trial information leaflets had been distributed to the patients. The details of the study were explained to the participants in the leaflets and posters. The participants had been included only if they meet the inclusion criteria and provide written informed consent.

Patients who met the following inclusion criteria were eligible for the study: (a) diagnosed as having ischemic or hemorrhagic stroke; (b) diagnosis was confirmed with cerebral computed topographic scanning or magnetic resonance imaging; (c) diagnosed as having depression with a score of 17 or greater in the 17-item Hamilton Rating Scale for Depression (HAMD-17); (d) men or women aged 30 to 75 years old; (e) willing to give voluntary, written informed consent before joining in the trial.

Patients who met any of the following criteria were excluded from the study: (a) presence of severe aphasia, especially fluent aphasia; (b) presence of severe cognitive dysfunction; (c) history of psychiatric illness other than depression; (d) presence of another chronic disorder, including severe Parkinson’s disease, cardiac disease, cancer, epilepsy, or chronic alcoholism; (e) having impaired hepatic or renal function; or (f) having bleeding tendency.

Grouping

One hundred and five patients were randomly divided into three groups with 35 for each group: Thin WAA group (Thin WAA needle + Fluoxetine), Thick WAA group (Thick WAA needle + Fluoxetine), and Sham WAA group (sham WAA needle + Fluoxetine). We made random assignment cards with number, group, random number and treatment method on it. The random assignment card was sealed with an envelope. The envelope number was the same as the card number. The envelopes were sorted by number and were held by a person. When a qualified participant entered the study, the treatment was given in groups according to the requirements of the card, and no change was allowed (Figure 1).

Acupuncture equipment

Thin WAA needle : 0.25 mm in diameter and 25 mm in length, Suzhou Medical Appliance Factory, Suzhou, China.

Thick WAA needle : 0.35 mm in diameter and 25 mm in length, Suzhou Medical Appliance Factory, Suzhou, China.

Sham WAA needle : 0.25 mm in diameter and 25 mm in length, Suzhou Medical Appliance Factory, Suzhou, China.

Treatment procedures

Fluoxetine: the fluoxetine hydrochloride was given to subjects once a day for 4 consecutive weeks (fluoxetine hydrochloride, 20 mg, the United States Lilly, batch No. 0935A).

WAA: WAA was performed on point upper 1 of both wrists (the front of the ulnar edge near the little finger where people can touch a sag). The needles were retained in the subcutaneous tissue for 30 min (Figure 2). The subjects were asked to stay in a sitting position, wearing an eye mask. The target point was disinfected...
with an iodophor disinfectant (Shanghai Likang Disinfectant Hi-tech Co., Ltd., Shanghai, China). The processed needles (thin or thick according to the group) were held with three right-hand fingers (thumb, index and middle finger). The skin near the target point was gently pressed with the left thumb to make it slightly taut. Then, the tip of the needle was swiftly inserted into the skin at the target point at an angle of 30°. The needle was lowered to the horizontal position and slowly advanced until the entire needle (except the handle) entered the subcutaneous tissue. The handle was then fixed to the skin with an adhesive tape. The needles were retained in the subcutaneous tissue for 30 min.

For a successful WAA treatment, the patient only felt a negligible stabbing pain when the tip of the needle pierced the skin. No other needling sensation was felt.

A single registered acupuncturist, with at least 1 year of previous WAA experience, administered the care to all subjects.\(^{33,34}\)

The intervention was conducted once a day for 6 consecutive days in a week, and the treatment lasted for 4 weeks.

**Sham WAA**: the patient was acupunctured on point upper 1 (the front of the ulnar edge near the little finger in where people can touch a sag) of both wrists. The patient was not allowed to see the needle during the needling process. The skin near the target point was gently pressed with the left humb to make it slightly taut. The tip and most part of the needle (0.25 mm in diameter and 25 mm in length, Figure 3) was cut off and blunted, with only 2 mm of the needle remained. The needle was held with three right-hand fingers. The needle tip swiftly hit the target point at a angle 30° (the tip was not actually inserted into the skin). Then, the needle remained horizontally on the skin of the point for 30 min. The handle was fixed to the skin with adhesive tape. For a successful sham treatment, the patient would also only feel a negligible stabbing pain when the tip of the needle hit the skin. No other needling sensation would be experienced. The intervention was conducted once a day for 6 consecutive days in a week, and the treatment lasted for 4 weeks.

**Clinical assessment**

Primary outcome: the subjects’ depression was measured by HAMD (17 items in all, including sleep, diet, depression, anxiety, etc.) before the treatment and at the end of weeks 1, 2, 3, 4, and 8 (follow-up week).

Secondary outcomes: the SDS data (20 items in all, including depression, sleep, heterosexual contact feeling, fatigue, anxiety, suicide status) were collected before the treatment and at the end of weeks 1, 2, 3, 4.

The QOL data (including sleep, self-satisfaction, sexual life, daily life, negative feelings, family and social relationships, etc.) were collected to take the patients’ quality of life into consideration before the treatment and at the end of week 4.

**Ethics approval**

The trial has been approved by the Ethics Committee of Shanghai Changhai Hospital and the approval document number is CHEC2015-015. This trial has been clinically registered and the registration number is ChiCTR-IOR-15006313.
The three groups differed in the time when the treatment started to have effect, and the SDS score difference was statistically significant compared with that before the treatment ($P < 0.05$).

### Depression self-rated

In the third and fourth treatment week, SDS score of thick WAA group and thin WAA group had statistically significant difference compared with that of the sham WAA group ($P < 0.05$). At any point of time, the SDS score was not statistically significant between thin WAA group and thick WAA group ($P > 0.05$) (Table 2).

### Quality of Life

Before treatment, there was no significant change in the quality of life in the three groups ($P > 0.05$). After four weeks of treatment, there was no statistically significant difference in QOL scale in the three groups after the treatment ($P > 0.05$) (Table 3).

#### DISCUSSION

PSD not only affects the recovery of limb function,
but also causes the recurrence of stroke. It has been proved that WAA combined with fluoxetine in the treatment of PSD has relatively good effects in clinical practice. WAA therapy can improve the treatment effect of fluoxetine, reduce drug adverse reactions in nerves and digestive tracts.\(^5\) This study aims to further verify the efficacy of WAA combined with fluoxetine in the treatment of PSD by observing whether it can enhance the efficacy and reduce the side effects of fluoxetine, and determining whether the diameter of the needles has any impact on the results.

WAA is a method to treat disease with needles on specific areas of the wrist or ankle.\(^6\) It is formatted and developed gradually by following the meridian theory.\(^7\) Long-term clinical study has proved that it is effective for the recovery of body function and mental illness.\(^8\) The treatment is simple in that only certain acupoints are treated. It is also gentle and the patient hardly feels any pain or damage to the body. According to WAA’s unique theoretical system, it has many advantages in relieving various types of anxiety. It does not generate any needling sensation, such as soreness, numbness, distention, or pain.\(^8\) Also, for some patients it is more acceptable than common filiform needle intervention. Therefore, a randomized, controlled and single-blind trial could be innovatively designed with a nonpenetrating sham WAA group, which was able to provide reliable evidence for WAA treating PSD.

WAA was invented in the 1970s and the needle was normally larger than 0.35 mm × 25 mm at that time. Later the needle diameter became smaller, and the patient felt less discomfort. Currently the commonly used needle is 0.25 mm × 25 mm, but it is still unclear whether the needle diameter has any impact on the efficacy of WAA. In this research the 0.35 mm × 25 mm and 0.25 mm × 25 mm needles were applied to observe whether the diameter has impact on the effect.

The results of this study showed that there was no significant difference between the thick WAA group and thin WAA group in HAMD scores between the two groups (4 w). The SDS score (3 w), FIM scale score (4 w) and SERS score (4 w) showed that needles with diameters of 0.35 and 0.25 mm made no difference. It has also been reported that placebo in patients with PSD is also effective.\(^9\) To eliminate the comfort effect of acupuncture, the study set a sham WAA group. The feeling of patients in the sham WAA group was same as the other two groups. The results showed that WAA combined with fluoxetine had obvious effect on patients’ depression treatment. The patients’ depression condition became better than that before treatment in their self-subjective cognition.

Regarding the discomfort brought about by acupuncture, thick WAA group had 1 case of sticking of needles and 1 case of hematoma; thin WAA group had 2 cases of bent needles. All this may occur in routine acupuncture treatment and we need to improve the acupuncturists’ skills to avoid these adverse events.

The present study also had a limitation. The trial only reflected the treatment effects under certain circumstances. The QOL-BREF scale should have included more factors such as the patient’s history and development of the disease. Besides, the scale also involved some subjective and psychological aspects, which awaits further study.

In conclusion, the present study showed that WAA combined with fluoxetine in the treatment of PSD could relieve the symptoms of depression after stroke. WAA therapy could improve the antidepressant effect of fluoxetine.

**REFERENCES**


