The effectiveness of acupuncture therapy in patients with post-stroke depression
An updated meta-analysis of randomized controlled trials

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Abstract

Background: To assess the effectiveness of acupuncture in patients with post-stroke depression (PSD).

Methods: The Cochrane Library, CINAHL, EMBASE, PubMed, SCOPUS, Web of Science, and 4 Chinese databases were electronically searched for articles published between January 1, 2010 and May 31, 2018. Randomized controlled trials (RCTs) investigating the effects of acupuncture on PSD were included. The quality of all included trials was assessed according to guidelines published by the Cochrane Collaboration.

Results: Seven trials compared the effectiveness of acupuncture therapy with that of control in alleviating the symptoms of PSD. Pooled analysis demonstrated that patients in the acupuncture intervention group experienced a significantly higher treatment effect than controls (RR 1.16 [95% CI 1.08–1.24]; P < .0001), with low study heterogeneity (I² = 4%). Based on intervention methods, further analysis revealed a statistically significant difference in effectiveness between the acupuncture alone and medicine groups (RR 1.25 [95% CI 1.11–1.41]; Z = 3.78; P = .0002). There was no statistically significant difference in efficacy between the acupuncture combined with medicine and medicine groups (RR 1.07 [95% CI 0.98–1.17]; P = .11).

Conclusions: This meta-analysis provides evidence supporting the viewpoint that acupuncture is an effective and safe treatment for PSD. Subgroup analyses further revealed that acupuncture alone resulted in better outcomes than drug therapy in improving depressive symptoms. Further high-quality RCTs are needed to systematically evaluate the effectiveness of acupuncture for PSD and develop standardized acupuncture protocols.

Abbreviations: BDNF = brain-derived neurotrophic factor, CI = confidence interval, Hamilton HRSD = rating scale for depression, PSD = post-stroke depression, RCTs = randomized controlled trials, RR = risk ratio.

Keywords: acupuncture, meta-analysis, post-stroke depression

1. Introduction

Stoke is a thromboinflammatory disease with a relatively high mortality and is a main cause of serious long-term disability; its key feature is hemostatic disturbances.[1,2] Post-stroke depression (PSD) is the most frequent neuropsychiatric sequela of stroke in patients, with a prevalence ranging from 29% to 35%.[1,2] Moreover, PSD negatively affects social activities, cognitive function, and stroke rehabilitation, which is closely associated with increased mortality.[3,4] Thus, it is important to reduce PSD in stroke survivors. Several therapeutic methods have been demonstrated to be effective for PSD, including pharmacological and non-pharmacological interventions (e.g., psychotherapy), and combination therapies.[5,6] The most frequently studied agents are antidepressants, among which selective serotonin reuptake inhibitors (e.g., fluoxetine) and serotonin and norepinephrine reuptake inhibitors are most prominent. However, the use of antidepressants in patients with PSD carries the risk of adverse events that may lead to blurry vision, urinary retention, sexual dysfunction, tremor, hypotension, and severe insomnia.[7,8] On the other hand, the use of antidepressants could also increase the risk of drug-drug interactions because most patients concurrently take other types of drugs.[9]

Acupuncture therapy has gradually attracted increasing attention as a part of non-drug therapy. Currently, several clinical trials have demonstrated that acupuncture treatment for PSD is significantly effective and has few side effects.[10,11] A systematic review and meta-analysis suggested that acupuncture may be superior to antidepressants in terms of clinical effectiveness and reducing depressive symptoms of patients with PSD.[12] However, numerous clinical studies aimed at evaluating the effectiveness of acupuncture in patients with PSD have been reported in recent years. The present meta-analysis was performed to evaluate the effectiveness rate of acupuncture therapy for depression in patients with PSD. The purpose was to present an updated overview of the literature in this area and provide evidence to healthcare professionals treating PSD for future reference.
Fifteen RCTs were included in a previous study and considered in a comprehensive review by Zhang et al. in a quantitative reassessment of articles published up to 2010. They reported that there was no difference in the effectiveness rate between the acupuncture and western medicine groups in the treatment of PSD. We aimed to update the current evidence by performing a meta-analysis of RCTs published between 2010 and May 2018 to evaluate the effectiveness rate of acupuncture in treating PSD and to provide doctors treating PSD with evidence for their reference.

2. Methods

2.1. Protocol and registration

This study was approved by the Institute Review Board of College of Nursing, Jilin University (access number: 2018031105). The present meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure comprehensive and transparent reporting of methods and results.

2.2. Search strategy

The CINAHL, the Cochrane Library, Embase, PubMed, SCOPUS, Web of Science, and four Chinese databases (CBM, CNKI, WanFang Data, and VIP) were electronically searched for articles published between January 1, 2010 and May 31, 2018. The search strategy included various combinations of the terms “depression,” “post-stroke depression,” and “PSD,” with acupuncture intervention terms including “acupuncture” or “electroacupuncture” or “moxibustion” or “acupuncture point” or “acupoint.” RCTs were specifically targeted using the following search terms: “Randomized controlled trial”, “Controlled clinical trial”, or “Randomized” or “Randomly” or “Trial” or “Group”. Only peer-reviewed articles and RCTs were included, and the search was limited to human studies. A manual search of references cited by the original published studies and relevant review articles was also performed. A search of Google Scholar was assisted by using the same key words to identify any additional relevant articles.

2.3. Eligibility criteria

Eligible studies were selected for the present meta-analysis based on the following criteria: RCTs; participants were adults (≥18 years of age) who met the criteria for standardized diagnosis of PSD as detailed in the Diagnostic and Statistical Manual of Mental Disorders or Chinese Classification of Mental Disorders and evaluated using the Hamilton Rating Scale for Depression (HRSD); studies in which the inclusion criteria included the intervention group that underwent acupuncture and a control group that did not undergo acupuncture intervention; and studies were required to report the effectiveness rate as the outcome measure. Studies involving participants with language difficulties, expression barriers, a history of depression, and/or allergy to acupuncture were excluded.

2.4. Study selection

The study selection process is described in Figure 1. The eligibility assessment was performed by 2 independent reviewers. All articles retrieved using the search strategy were assessed for eligibility based on the previously defined inclusion criteria by reviewing their titles and/or abstracts. If this information was insufficient to evaluate the inclusion or exclusion of an article, then a full-text version was obtained. Full-text versions of all relevant studies were obtained and reviewed by 2 independent reviewers. When differences regarding eligibility for inclusion,
exclusion, or data extraction occurred, a third reviewer participated in the discussion. If the information or data in the included articles was insufficient, the authors of the studies were contacted to obtain additional information.

2.5. Quality assessment

Two investigators independently reviewed the quality of the included studies. Discrepancies were resolved by discussion with another author. The quality items assessed included: random sequence generation; allocation concealment; blinding (participants, personnel, and outcome assessment); completeness of follow-up; selective reporting; and intention-to-treat analysis. Each study was classified as low risk, unclear risk, or high risk following the criteria described in the Cochrane Handbook for Systematic Reviews of Interventions.

2.6. Data extraction and synthesis

Data extraction was conducted independently by the same investigators using standard data extraction forms. One investigator performed the data extraction, which was verified by another investigator. The data extraction form summarized major characteristics, including information about the participants, sample size, mean age, intervention, control group sizes, and outcomes. Detailed information about the acupuncture intervention and control group were extracted and included acupuncture points, type of acupuncture, intervention cycle, and frequency of intervention. The final outcomes were reported to evaluate the effectiveness rate of acupuncture on PSD in every RCT.

Review Manager version 5.3 (Cochrane Collaboration, Oxford, United Kingdom) software was used to estimate the overall effect of acupuncture therapy and generate forest plots in this study. The intervention effect was described as a risk ratio (RR) with the corresponding 95% confidence interval (CI) for dichotomous outcomes. Selection of fixed or random effects models were based on the potential real effect of the intervention on outcome measures. I² < 25% was considered to be low-level heterogeneity, 25% to 50% as moderate, and >50% as high heterogeneity. A fixed effects model was used to calculate summary estimates in the absence of significant heterogeneity. For all analyses, P < .05 was considered to be statistically significant.

3. Results

Initially, 158 articles were retrieved from the database search; after removal of duplicates, 107 remained. Based on title and abstract, 75 studies were excluded. The full-text articles of 32 studies were reviewed and 25 were excluded due to the following reasons: acupuncture combined with music therapy (n=7); review articles (n=3); control group underwent an acupuncture intervention (n=6); or did not use the effectiveness rate as an outcome measurement (n=9). Finally, 7 studies[12-18] with 514 participants were included in the final analysis (Fig. 1).

The 7 RCTs provided sufficient data for statistical pooling. The characteristics of these trials are summarized in Table 1. Samples sizes in the included studies ranged from 43 to 100, and mean participant age ranged from 56 to 69 years; however, 1 study did not report mean age. Patients were diagnosed with PSD using

| Table 1 | Characteristics of included studies. |
|---------|--------------------------------------|
| **Article** (year) | **Sample characteristics** | **Interventions** |
| Liu18 (2013) | RCT | IG = 30 | CG = 30 | IG = 69 ± 5 | CG = 68 ± 5 | Acupuncture combined with moxibustion | Fluoxetine | Bilateral BL14, BL15, BL17, BL18, BL20, BL22, BL23 | 20 days | 6week, 25 min | ≥25% |
| Li17 (2011) | RCT | IG = 23 | CG = 20 | IG = 56.7 ± 14.4 | CG = 59.4 ± 12.1 | Acupuncture + placebo | Fluoxetine- non-acupoint acupuncture | GV 20, GV29, EX-HN 1, 6 weeks | LR 3.HT 7.KI 3. BL 15, PC 6.SF 6 | 5week, 30 min | ≥50% |
| Cao13 (2014) | RCT | IG = 30 | CG = 30 | IG = 56.57 ± 10.15 | CG = 57.13 ± 10.74 | Citalopram Hydrobromide tablets+ acupuncture | Citalopram Hydrobromide tablets | Bilateral BL21, BL20, BL17, CV12, CV4, ST36, ST40 | 4 weeks | 6week, 30 min | ≥25% |
| Liao16 (2017) | RCT | IG = 50 | CG = 50 | IG = 56.0 ± 16.5 | CG = 56.0 ± 15.5 | Fluoxetine+ acupuncture combined with moxibustion | Fluoxetine | GV20, CV6, CV7, RN4, GV26, GV24, LR14, LR9, KI 3, EX-HN 1, ST36, ST40 | 20 days | 1/day, 30 min | ≥30% |
| Chu15 (2017) | RCT | IG = 50 | CG = 50 | IG = 61.54 ± 2.63 | CG = 60.3 ± 2.51 | Acupuncture | Routine medication | HT7, GB30, BL48, BL46, BL44, BL47, LR 3 | 24 days | 3week, 30 min | ≥30% |
| Yan14 (2018) | RCT | IG = 50 | CG = 50 | IG = 62.1 ± 13.3 | CG = 62.3 ± 13.6 | Acupuncture combined with moxibustion +venlafaxine hydrochloride sustained-release tablets | Venlafaxine hydrochloride sustained-release tablets | MS1, GV 20, EX-HN 1, 4 weeks | BL15, BL13, BL18, BL20, BL23 | 6week, 30 min | ≥25% |
| Sun12 (2015) | RCT | IG = 27 | CG = 24 | 56.8 | Electroacupuncture | Traditional Chinese medicine | AT3, HT7, CO15, CO12, 6 weeks | C010 | 6week, 30 min | ≥25% |

AT3 = Naogan, BL14 = Jueyinshu, BL13 = Fengshu, BL15 = Xumi, BL17 = Geshu, BL18 = Gaishu, BL20 = Fushu, BL21 = Weishu, BL22 = Sanjiaoshu, BL23 = Shenhu, BL44 = Shenting, BL48 = Hegu, BL47 = Huping, BL48 = Yanggang, CG = control group, CG10 = Shen, CG12 = Gan, CG15 = Xi, CV = Xueji, CV6 = Gvah, CV7 = Yinjiao, CV12 = Zhongyuan, CV17 = Zhongtang, EX-HN 1 = Sishencong, GB30 = Shenting, GV20 = Baihui, GV24 = Shenting, GV26 = Renchong, GV29 = Yingxiang, HT7 = Shenmen, IG = intervention group, KI3 = Taiji, KI3 = Taichong, LR14 = Qimen, MS1 = Ezhongxian, P06 = Neiguan, RCT = randomised controlled trial, RN4 = Guanyuan, SP6 = Sanyinjiao, ST36 = Zusanli, ST40 = Fenglong.
imaging and HRSD. Among the included studies, 4 reported interventions with traditional acupuncture, 1 used electroacupuncture treatment, and 2 used acupuncture combined with moxibustion. The interventions were performed under the management of trained, experienced acupuncture practitioners. The choice of acupuncture points among the various studies differed. Three studies assessed the effectiveness rate by comparing acupuncture with drug therapy. Four studies examined acupuncture therapy combined with drug therapy, and the control group was drug therapy alone. The duration of therapy ranged from 20 days to 6 weeks. The most common frequency of intervention was 6 times per week and duration was 30 minutes. Demographic data from the 2 groups were compared and were not statistically different in any trial ($P > .05$).

### 3.1. Risk of bias assessment

A quality assessment of each domain among the seven included studies is presented in Figure 2. Most ($n = 6$) of the studies had a high risk of bias. Major sources of bias were from a lack of blinding study subjects or research personnel, selective reporting, and blinding of outcome assessment. Of the 7 studies, 6 described the method of randomization, and not all studies described the method of sequence generation or allocation concealment. Due to the nature of the exercise intervention, it may be difficult to blind participants to intervention delivery. Only 1 study was double-blinded, and four other trials attempted to blind the outcome assessors to minimize potential methodological bias. Six studies did not report adverse events, which may have introduced potential reporting bias.

### 3.2. Outcomes

#### 3.2.1. Main analysis

Seven trials assessed the effectiveness rate of acupuncture therapy versus controls in alleviating the symptoms of PSD. The HRSD scale was used as standard for evaluating depression in all studies. The effectiveness rate was defined as a reduction of $\geq 25\%$ in the total HRSD score, calculated according to the scale score before and after treatment as follows:

$$\text{Reduction rate} = \frac{\text{posttreatment score} - \text{pretreatment score}}{\text{pretreatment score}} \times 100$$

Pooled analysis demonstrated that patients in the acupuncture intervention group experienced significantly higher treatment effects than controls (RR 1.16 [95% CI 1.08–1.24]; $P < .0001$), with low heterogeneity ($I^2 = 4\%$) (Fig. 3).

#### 3.2.2. Subgroup analysis

Based on intervention methods, 2 subgroup analyses were conducted. There were 4 studies that compared the effectiveness rate between acupuncture combined with a medicine group and a medicine alone group. Pooled analysis revealed no statistically significant differences in efficacy between the 2 groups (RR 1.07 [95% CI 0.98–1.17]);
Three studies\textsuperscript{[18–20]} compared the effectiveness rate between acupuncture alone and the medicine group (merged RR 1.25 [95% CI 1.11–1.41]) (Fig. 4). Tests for overall effect revealed a statistically significant difference in effectiveness rate between the acupuncture alone and medicine groups ($Z = 3.78$ and $P = .0002$).

3.3. Adverse events

Of the 7 included RCTs, only one reported adverse effect related to acupuncture interventions. Li et al\textsuperscript{[19]} reported there were 3 cases in the control group and intervention group, each, after treatment. Adverse reactions in the intervention group included subcutaneous continuous pain, dizziness, and nausea, and subcutaneous hematoma after acupuncture. Adverse effects in the control group included dizziness after treatment, arm numbness, and palpitation after acupuncture. However, the adverse reactions were transient, and there was no significant difference in the rate of adverse events between the 2 groups ($P > .05$).

4. Discussion

Acupuncture is one of the most popular non-drug therapies in the West. Accumulating evidence suggests that acupuncture has been used clinically for PSD; however, to date, results of studies have been inconsistent regarding the effectiveness rate of acupuncture in improving depression in PSD patients. A recent meta-analysis shows that there was a statistical difference in the curative rate between the acupuncture group and medicine group when treating PSD, but due to the sole focus on the comparison of curative rates without analysis of the effective rate or adverse incidents, the evidence was limited by the non-comprehensive evaluation. In the present study, 7 of the strictly-designed randomized controlled trials, including 514 patients, involving acupuncture therapy were identified for meta-analysis. However, contrary to the conclusion of a previous meta-analysis,\textsuperscript{[21]} our updated meta-analysis confirms that acupuncture intervention resulted in better outcomes when compared with the medicine groups in improving depressive symptoms in PSD patients and without any obvious adverse reactions.

It is difficult to achieve complete remission of PSD using conventional antidepressants, which also lead to many adverse effects such as cardiovascular or gastrointestinal side effects, sleep disturbance, and sexual dysfunction.\textsuperscript{[22]} In recent years, investigations of treatment of PSD using acupuncture have gradually achieved satisfactory results. However, the pathogenesis of PSD currently remains unclear. The mechanism of action of acupuncture for the treatment of PSD may be the result of multiple targets and multi-level effects. Studies have found that acupuncture can increase the brain levels of the monoamine neurotransmitters 5-hydroxytryptamine, dopamine, norepinephrine, and acetylcholine; therefore, substances such as gamma-butyric acid can exert their antidepressant effect.\textsuperscript{[23]} There is a theory that acupuncture can reduce the levels of inflammatory cytokines, such as interleukin-6, and the concentration of tumor necrosis factor-$\alpha$ in the serum reduces inflammation and exerts antidepressant effects.\textsuperscript{[24]} A large number of clinical studies and animal experiments have demonstrated the relationship between abnormal expression of brain-derived neurotrophic factor (BDNF) and occurrence of depression.\textsuperscript{[25]} The development of acupuncture can play a role in mitigating depressive symptoms by increasing BDNF levels in the serum of PSD patients.\textsuperscript{[26]}

In subgroup analyses based on intervention methods, there was a statistically significant difference in the effectiveness rate in PSD patients between the acupuncture alone and medicine groups; however, acupuncture combined with medicine was not observed to be effective. This result was unexpected. A possible underlying
reason may be the small number of included studies; thus, more evidence is required for the effect of acupuncture combined with medicine. Another likely possibility is that most of the included studies performed 4-week acupuncture interventions. Because of the short duration of the intervention, we may not be able to draw a conclusion on the effect of acupuncture combined with medicine. While acupuncture interventions demonstrate positive effects on PSD, we found that the evaluation standards for effectiveness rate were different in each study. Most studies reported an effectiveness rate of ≥25% or ≥30%. There is presently no definitive standard regarding this issue. Therefore, this appears to affect the evaluation of effectiveness rate outcomes to some extent.

In the included studies, it is worth noting that one double-blind RCT reported that the efficacy of the acupuncture group was similar to that of the drug group. The observation group was treated with acupuncture combined with oral placebo, compared with non-acupoint shallow punctures combined with oral fluoxetine. This may be due to the proximal acupoint shallow acupuncture control used in this study, which may also produce a certain degree of efficacy and enhance effects in the control group. One study used functional magnetic resonance techniques to study the effects of acupuncture points and non-acupoints on brain function, thereby exploring the specificity of acupoint stimulation effects. It was found that most of the brain regions associated with acupuncture and non-acupoint brain function share similar connections.[27] Another study also demonstrated the similarities in biochemical and neuroimaging changes induced by stimulation of specific and nonspecific acupoints.[28] These similarities could only partially explain the differences in effects between sham and active acupuncture.

Numerous studies have found that activation of brain regions and intensity are associated with manipulation type, acupoint locations, stimulation paradigms, needing depth, and stimulus duration.[29] One study reported that patients with PSD who underwent higher frequency acupuncture treatments may have experienced greater improvement of depressive symptoms.[30] Because of the small number of studies, we cannot compare the effects of electroacupuncture, acupuncture combined with moxibustion, and traditional acupuncture. Moreover, the selection of acupoints in the included studies was not the same and, therefore, further research to optimize acupoint selection and improve the therapeutic schedule is warranted. How to achieve the best curative effect with the smallest stimulation and most optimized therapeutic schedule will be the focus of future research.

There were several limitations to the present study, the first of which is the small sample size and assessment based only on a single HRSD scale, both of which may reduce the accuracy of the analyses and result in overestimating the overall effects. Furthermore, many trials included in the present analysis did not design blinding protocols or placebo or sham acupuncture to exclude the psychological effects of acupuncture. Therefore, caution should be exercised when interpreting the results. Second, a large portion of the trials included in this study did not provide detailed demographic or methodological information, such as medication history, duration of illness, number of mood episodes, random sequence generation method, and intention-to-treat analyses. We could not determine associations between treatment effects and demographic factors and potential biases derived from methodological flaws. Finally, most of the patients involved in the studies were Asian and, therefore, the results are not necessarily representative of a larger, wider population. Designing a large-sample, multicenter study with strict implementation of allocation concealment and blinding evaluation are potential future directions for research.

5. Conclusion
This meta-analysis provides evidence to support the viewpoint that acupuncture is an effective and safe treatment for PSD. Subgroup analyses further revealed that acupuncture alone produced better outcomes than drug therapy in improving depressive symptoms. However, due to the small number of available studies, it is not currently possible to make any recommendations for acupuncture in the treatment of PSD. Further high-quality RCTs are needed to systematically evaluate the effectiveness of acupuncture for PSD and develop standardized acupuncture protocols.

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