Efficacy of kidney-tonifying and brain-strengthening acupuncture therapy combined with sertraline for geriatric depression: A Randomized Controlled Trial postprint

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Abstract

Background Depression in Traditional Chinese Medicine falls under the category of emotional diseases, and its pathogenesis can be explained by the "Kidney-Brain Mutual Promotion" theory. Whether Bushen Jiannao acupuncture therapy can be used to treat geriatric depression has not been previously reported.

Objective To investigate the efficacy of Bushen Jiannao acupuncture therapy based on the "Kidney-Brain Mutual Promotion"theory combined with sertraline in improving mood and cognitive function in elderly patients with depression.

Methods This trial was registered with the Chinese Clinical Trial Registry (registration number: ChiCTR2400081227). A total of 86 elderly patients with depression admitted to the Department of Psychiatry and Psychology at the General Hospital of Northern Theater Command from March 2023 to March 2024 were enrolled and randomly divided into an observation group (n=43) and a control group (n=43). The control group received sertraline treatment, while the observation group received Bushen Jiannao acupuncture combined with sertraline for a total of 4 weeks. Before and after treatment, the 17-item Hamilton Depression Rating Scale (HAMD-17) was used to assess depressive mood; the Wisconsin Card Sorting Test was used to evaluate cognitive function; platelet count (PLT), monocyte count (MONO), neutrophil count (NC), and lymphocyte count (LC) were measured, and the systemic immune-inflammation index (SII) and systemic inflammatory response index (SIRI) were calculated. HAMD-17 scores, cognitive function, SII, and SIRI were compared between the two groups before and after treatment. Pearson correlation analysis was used to examine the relationship between changes in HAMD-17 scores, changes in

cognitive function, and changes in SII and SIRI in the observation group before and after treatment. The clinical efficacy of the two groups was compared.

Results After treatment, the HAMD-17 score in the observation group was lower than that in the control group (P<0.05), the percentage of correct responses and the percentage of conceptual level in the Wisconsin Card Sorting Test were higher than those in the control group (P<0.05), and SII and SIRI were lower than those in the control group (P<0.05). In the observation group, the change in SII before and after treatment showed a linear positive correlation with the change in HAMD-17 score (r=0.536, P<0.05), and a linear negative correlation with the percentage of correct responses (r=-0.621, P<0.05) and the percentage of conceptual level (r=-0.482, P<0.05) in the Wisconsin Card Sorting Test. The change in SIRI before and after treatment showed a linear positive correlation with the change in HAMD-17 score (r=0.429, P<0.05), and a linear negative correlation with the percentage of correct responses (r=-0.378, P<0.05) and the percentage of conceptual level (r=-0.434, P<0.05) in the Wisconsin Card Sorting Test. The clinical efficacy of the observation group was superior to that of the control group (P<0.05).

Conclusion Bushen Jiannao acupuncture therapy can enhance the therapeutic effect of sertraline in treating geriatric depression, and its mechanism for alleviating depressive mood and cognitive dysfunction may be related to the improvement of immune-inflammatory status.

Full Text

The Effect of Kidney-Tonifying and Brain-Strengthening Acupuncture Combined with Sertraline in the Treatment of Late-Life Depression: A Randomized Controlled Trial

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Abstract

Background: Depression falls under the category of emotional disorders in traditional Chinese medicine (TCM), and its pathogenesis can be explained by the theory of "kidney-brain mutual nourishment." However, whether kidney-tonifying and brain-strengthening acupuncture therapy can be used to treat late-life depression has not been previously reported.

Objective: To investigate the efficacy of kidney-tonifying and brain-strengthening acupuncture therapy, based on the theory of "kidney-brain

mutual nourishment," combined with sertraline in improving mood and cognitive function in elderly patients with depression.

Methods: This trial was registered with the Chinese Clinical Trial Registry (registration number: ChiCTR2400081227). Eighty-six elderly patients with depression admitted to the Department of Psychiatry of the General Hospital of Northern Theater Command between March 2023 and March 2024 were enrolled and randomly divided into an observation group (n=43) and a control group (n=43). The control group received sertraline alone, while the observation group received kidney-tonifying and brain-strengthening acupuncture combined with sertraline. Both groups were treated for 4 weeks. Before and after treatment, depressive mood was assessed using the 17-item Hamilton Depression Rating Scale (HAMD-17), cognitive function was evaluated using the Wisconsin Card Sorting Test, and platelet count (PLT), monocyte count (MONO), neutrophil count (NC), and lymphocyte count (LC) were measured to calculate the systemic immune-inflammation index (SII) and systemic inflammatory response index (SIRI). Changes in HAMD-17 scores, cognitive function, SII, and SIRI were compared between the two groups. Pearson correlation analysis was used to examine relationships between changes in HAMD-17 scores, cognitive function measures, and inflammatory indices in the observation group. Clinical efficacy was also compared between groups.

Results: After treatment, the observation group showed lower HAMD-17 scores ($P<0.05$), higher percentages of correct responses and conceptualization levels on the Wisconsin Card Sorting Test ($P<0.05$), and lower SII and SIRI values ($P<0.05$) compared to the control group. In the observation group, changes in SII were positively correlated with changes in HAMD-17 scores ($r=0.536$, $P<0.05$) and negatively correlated with percentages of correct responses ($r=-0.621$, $P<0.05$) and conceptualization levels ($r=-0.482$, $P<0.05$) on the Wisconsin Card Sorting Test. Similarly, changes in SIRI were positively correlated with changes in HAMD-17 scores ($r=0.429$, $P<0.05$) and negatively correlated with percentages of correct responses ($r=-0.378$, $P<0.05$) and conceptualization levels ($r=-0.434$, $P<0.05$). The clinical efficacy of the observation group was superior to that of the control group ($P<0.05$).

Conclusion: Kidney-tonifying and brain-strengthening acupuncture therapy can enhance the effectiveness of sertraline in treating late-life depression, and its mechanism for alleviating depressive symptoms and improving cognitive function may be related to modulation of immune-inflammatory responses.

Keywords: Depression; Aged; Acupuncture; Sertraline; Cognitive function; Systemic immune-inflammation index; Systemic inflammatory response index

Introduction

Depression is a common mental disorder in older adults, characterized by low mood, loss of interest, reduced activity, and cognitive impairment, which impacts social functioning and places a burden on families. Clinically, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are commonly used to treat late-life depression, but these approaches have limitations including modest efficacy, significant adverse effects, and poor treatment adherence. Acupuncture, as a traditional Chinese medicine modality, has attracted considerable attention for treating late-life depression. Research indicates that acupuncture can improve depressive symptoms by modulating central synaptic plasticity, neuroendocrine function, and neurotransmitter systems. Additionally, acupuncture may exert antidepressant effects by ameliorating inflammatory damage, with studies showing significant improvements in serum levels of inflammatory cytokines such as interleukin-10 (IL-10) and interleukin-1 (IL-1) following treatment.

In TCM, depression belongs to the category of emotional disorders, and its pathogenesis can be explained by the theory of "kidney-brain mutual nourishment." The kidney stores innate essence, and kidney essence can nourish the brain and generate marrow. This essence is the root of all organ systems, and maintaining kidney essence provides the material basis for nourishing the brain. Individuals with robust kidney qi have abundant brain marrow and normal brain function, manifesting as clear consciousness and spirited demeanor. Conversely, deficiency of kidney essence leads to emptiness of the sea of marrow, subsequently affecting mood and brain function. Our research group previously found that kidney-tonifying and brain-strengthening acupuncture therapy based on this theory could improve mood and quality of life in patients with depression. However, whether this acupuncture approach is effective for late-life depression has been rarely reported. Sertraline is a commonly used medication for treating late-life depression. This study investigated the effects of kidney-tonifying and brain-strengthening acupuncture combined with sertraline on mood and cognitive function in elderly patients with depression.

The systemic immune-inflammation index (SII) and systemic inflammatory response index (SIRI) reflect the balance between inflammatory and immune responses. Higher levels of these indices correlate with greater severity of depression and more severe cognitive impairment. This study examined changes in SII and SIRI before and after treatment to explore potential mechanisms underlying acupuncture treatment for late-life depression.

Methods

1.1 Study Participants

Sample size was calculated using PASS 2021 software. Based on a superiority margin of 16 for HAMD-17 scores from pilot data, with α=0.05 and β=0.20, the required sample size was determined to be at least 39 participants per group. Considering potential attrition, the final sample size was set at 43 participants per group. Between March 2023 and March 2024, 86 elderly patients with depression admitted to the Department of Psychiatry of the General Hospital of Northern Theater Command were enrolled and randomly assigned to either the observation group (n=43) or the control group (n=43) using a random number table method. Diagnosis of depression was based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).

Inclusion criteria were: (1) age $\geq$ 60 years; (2) first-time diagnosis or antidepressant discontinuation for more than 1 month; (3) no organic brain disease; and (4) ability to complete psychological assessments. **Exclusion criteria** included: (1) other psychiatric disorders such as substance use disorder, bipolar disorder, or schizophrenia; (2) severe physical illness; (3) infection; (4) metabolic disease; and (5) dementia or consciousness disturbance. **Dropout criteria** were: (1) severe adverse reactions or needle fainting; (2) worsening depression or emergence of suicidal ideation/behavior; and (3) voluntary withdrawal from the study.

This study was approved by the Ethics Committee of the General Hospital of Northern Theater Command [approval number: 伦审 Y(2023)035 号] and registered with the Chinese Clinical Trial Registry (registration number: ChiCTR2400081227).

1.2 Treatment Protocol

Patients in the control group received sertraline hydrochloride (Zhejiang Huahai Pharmaceutical Co., Ltd., National Drug Approval Number H20080141) with a target dose of 100 mg/day. Patients in the observation group received kidney-tonifying and brain-strengthening acupuncture in addition to sertraline. Both groups received continuous treatment for 4 weeks.

The acupuncture protocol involved: main acupoints at Baihui (GV20), Shenting (GV24), and Dazhong (KI4), with supplementary points at Fengchi (GB20), Neiguan (PC6), Shenmen (HT7), Zusanli (ST36), and Sanyinjiao (SP6). After skin disinfection with iodophor, 0.3 mm $\times$ 40 mm filiform needles were inserted using the even reinforcing-reducing technique. Needles were manipulated every 10 minutes, retained for 40 minutes per session, administered once daily, five days per week (Monday through Friday).

1.3 Outcome Measures

Before treatment and after 4 weeks of treatment, depressive mood was assessed using HAMD-17, cognitive function was evaluated using the Wisconsin Card Sorting Test, and SII and SIRI were calculated. Adverse events during treatment were also recorded.

(1) HAMD-17: This 17-item scale assesses depression severity, covering symptoms including depressed mood, guilt, suicidal ideation, sleep disturbance, work and interest reduction, and psychomotor retardation or agitation. Each item uses a 0-4 or 0-2 multi-level scoring system, with total scores ranging from 0-52. Scoring criteria are: $ $7 indicates no depression, 8-17 mild depression, 18-24 moderate depression, and $ $25 severe depression. In this study, the Cronbach' s α coefficient was 0.905.

(2) Wisconsin Card Sorting Test: This neuropsychological assessment tool evaluates abstract reasoning, cognitive flexibility, attention, working memory, information retrieval, category maintenance, category shifting, and stimulus processing by requiring participants to sort cards according to changing rules based on color, shape, or number. This study used the brief version (64 cards) and recorded the percentage of correct responses and conceptualization level.

(3) Inflammatory indices: Morning fasting venous blood samples were collected and analyzed using a DYN3700 automatic hematology analyzer (Abbott, USA) to measure platelet count (PLT), neutrophil count (NC), lymphocyte count (LC), and monocyte count (MONO). SII was calculated as PLT × NC / LC, and SIRI as MONO × NC / LC.

1.4 Clinical Efficacy Evaluation

Treatment efficacy was evaluated using the HAMD-17 reduction rate, calculated as: (pretreatment score - posttreatment score) / pretreatment score × 100%. A reduction rate >75% indicated recovery, 50-75% marked effectiveness, 25-50% effectiveness, and $ $25% ineffectiveness.

1.5 Statistical Analysis

Statistical analysis was performed using SPSS 20.0 software. Continuous variables are presented as mean ± standard deviation ($\bar{x}\pm s$) and compared between groups using independent samples t-tests. Within-group comparisons before and after treatment used paired t-tests. Categorical data are expressed as percentages and compared using ^{2} tests. Pearson correlation analysis examined relationships between changes in HAMD-17 scores, cognitive function measures, and inflammatory indices in the observation group. Mann-Whitney U test compared efficacy between groups. $P<0.05$ was considered statistically significant.

Results

2.1 Comparison of Baseline Characteristics

There were no statistically significant differences between the two groups in gender, marital status, disease duration, or BMI (P>0.05) .

2.2 Comparison of HAMD-17 Scores Before and After Treatment

Before treatment, HAMD-17 scores did not differ significantly between groups (P>0.05). After treatment, both groups showed significantly lower HAMD-17 scores compared to baseline (P<0.05), with the observation group demonstrating lower scores than the control group (P<0.05) .

2.3 Comparison of Cognitive Function Before and After Treatment

Baseline comparisons revealed no significant differences between groups in the percentage of correct responses or conceptualization level (P>0.05). Following treatment, both groups showed significant improvements in these measures (P<0.05), with the observation group achieving higher scores than the control group (P<0.05) .

2.4 Comparison of SII and SIRI Before and After Treatment

No significant baseline differences were observed between groups in SII or SIRI (P>0.05). After treatment, both indices decreased significantly in both groups (P<0.05), with the observation group showing lower values than the control group (P<0.05) .

2.5 Correlation Analysis Between Changes in HAMD-17, Cognitive Function, and Inflammatory Indices

In the observation group, the mean change in HAMD-17 score was -13.78 ± 1.88 points. Changes in Wisconsin Card Sorting Test measures were: correct response percentage increased by 19.20 ± 4.12%, and conceptualization level increased by 20.19 ± 4.58%. SII decreased by 61.18 ± 20.10, and SIRI decreased by 0.17 ± 0.09.

Pearson correlation analysis revealed that changes in SII were positively correlated with changes in HAMD-17 scores (r=0.536, P<0.001) and negatively correlated with percentage of correct responses (r=-0.621, P<0.001) and conceptualization level (r=-0.482, P<0.001). Similarly, changes in SIRI were positively correlated with changes in HAMD-17 scores (r=0.429, P<0.001) and negatively correlated with percentage of correct responses (r=-0.378, P<0.01) and conceptualization level (r=-0.434, P<0.01).

2.6 Comparison of Clinical Efficacy Between Groups

The observation group demonstrated superior therapeutic efficacy compared to the control group, with a statistically significant difference (Z=-2.856, P=0.020) .

2.7 Comparison of Adverse Reactions

There was no significant difference in the overall incidence of adverse reactions between the two groups (^{2}=0.567, P=0.451) .

Discussion

Late-life depression can lead to disability and cognitive dysfunction, warranting serious clinical attention. Commonly used SSRIs and SNRIs have limited efficacy, with approximately two-thirds of patients failing to achieve significant symptom relief after initial antidepressant treatment. Improving treatment outcomes for depression remains a critical concern in the field. This study found that kidney-tonifying and brain-strengthening acupuncture therapy can enhance the effectiveness of sertraline and improve cognitive function in elderly patients with depression.

From a TCM perspective, late-life depression primarily stems from kidney deficiency and decline, which fails to generate marrow and nourish the sea of marrow, resulting in loss of mental nourishment. Based on the "kidney-brain mutual nourishment" theory, kidney-tonifying and brain-strengthening herbal medicine can improve depressive symptoms and cognitive function in older adults. In this study, the observation group showed greater improvement in HAMD-17 scores than the control group, demonstrating that kidney-tonifying and brain-strengthening acupuncture can enhance sertraline' s therapeutic effects. The acupuncture protocol selected Baihui (GV20), Shenting (GV24), and Dazhong (KI4) as main points, with Fengchi (GB20), Neiguan (PC6), Shenmen (HT7), Zusanli (ST36), and Sanyinjiao (SP6) as supplementary points. Baihui, a governing vessel point, can tonify qi, lift yang, and fill the sea of marrow, thereby improving depressive symptoms and cognitive function. Shenting clears the head, dispels wind, and calms the spirit while enhancing cognitive function. Dazhong, a kidney meridian point, tonifies kidney qi and regulates the lower jiao. Fengchi pacifies liver wind and clears the head and eyes. Neiguan and Shenmen, as luo-connecting and source points respectively, regulate heart qi, unblock blood vessels, and treat mental disorders. Zusanli supplements qi and blood, while Sanyinjiao regulates kidney function to ensure proper generation of brain marrow. Our previous research using kidney-tonifying and brain-strengthening acupuncture combined with escitalopram oxalate for depression achieved similar positive results, with a treatment response rate of 93.33%.

Elderly patients with depression often experience cognitive dysfunction, includ-

ing memory decline, attention deficits, and reduced psychomotor speed. However, conventional antidepressants provide limited cognitive benefits and may even impair cognitive function. Previous studies have confirmed that acupuncture can improve cognitive function in patients with depression. This study used the Wisconsin Card Sorting Test to assess cognitive function. After treatment, both groups showed increased percentages of correct responses and conceptualization levels, with the observation group achieving higher scores than the control group. These findings indicate that kidney-tonifying and brain-strengthening acupuncture can improve cognitive function in elderly patients with depression. Previous research has also demonstrated that kidney-tonifying and brain-strengthening herbal medicine can improve cognitive function in post-stroke depression.

Immune-inflammatory damage represents an important pathological mechanism in depression. Inflammation contributes to depression development through effects on neuroendocrine function, brain neural circuits, synaptic plasticity, and epigenetics. Additionally, inflammatory damage is associated with cognitive impairment in depressed patients. Previous studies have confirmed that acupuncture can treat depression by alleviating inflammatory damage. Zhang et al. found that acupuncture can improve serum levels of inflammatory cytokines including TNF-α, IL-1α, IL-6, and IL-2 in patients with depression. Our previous research demonstrated that acupuncture can improve depressive-like behavior in mice by inhibiting the hippocampal NF- B/NLRP3 inflammatory pathway and reducing levels of TNF-α, IL-6, IL-1β, and IL-18. Unlike these specific cytokines, SII and SIRI derived from routine blood tests can reflect overall systemic inflammatory status and are clinically convenient to calculate. Previous studies have found that SII is significantly elevated in patients with depression compared to healthy individuals, positively correlating with depression severity and negatively correlating with cognitive function. Additionally, SIRI is higher in depressed patients and associated with suicidal ideation. This study found that both SII and SIRI decreased after treatment, with lower values in the observation group than the control group, suggesting that kidney-tonifying and brain-strengthening acupuncture can ameliorate immune-inflammatory damage in depression. Further analysis revealed positive correlations between changes in SII/SIRI and changes in HAMD-17 scores, and negative correlations between inflammatory index changes and cognitive test performance. These results suggest that acupuncture' s mechanisms for improving depressive symptoms and cognitive function may involve alleviating inflammatory damage.

Kidney-tonifying and brain-strengthening acupuncture based on the "kidney-brain mutual nourishment" theory can enhance sertraline' s effectiveness in treating late-life depression, with mechanisms potentially related to modulation of immune-inflammatory responses. This study has several limitations, including lack of long-term follow-up and direct measurement of peripheral immune cell function changes. Future research should examine the long-term effects of kidney-tonifying and brain-strengthening acupuncture and conduct animal studies to further elucidate its mechanisms of action.

Author Contributions: Li Li and Wang Qi conceived and designed the study and revised the manuscript. Xu Tianchao and Li Dongdong performed acupuncture treatments. Huang Hongfei, Cui Gang, Zhang Ou, and Fan Lin collected scale data and organized the dataset. Dong Xiaomei performed statistical analysis. Xu Tianchao provided guidance for the trial. Wang Qi supervised the study and took overall responsibility.

Conflict of Interest Statement: The authors declare no conflicts of interest.

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Note: Figure translations are in progress. See original paper for figures.