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# Efficacy of repetitive transcranial magnetic stimulation combined with horticultural therapy for post-stroke depression: A randomized controlled trial

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## Abstract

Post-stroke depression (PSD) affects approximately one-third of stroke survivors, and current treatments often present limitations. Non-invasive therapies such as repetitive transcranial magnetic stimulation (rTMS) and horticultural therapy (HT) are gaining interest as alternative approaches. This study aimed to evaluate the clinical efficacy of rTMS combined with HT in treating PSD. Eighty PSD patients (aged 30 – 75 years old; 1 month – 2 years post-stroke), diagnosed according to the Chinese Expert Consensus on Clinical Practice of Post-Stroke Depression, were randomly assigned to one of four treatment groups: Group A (antidepressant alone—escitalopram, 10 mg/day), Group B (antidepressant + rTMS), Group C (antidepressant + HT), and Group D (antidepressant + rTMS + HT). rTMS was administered to the left dorsolateral prefrontal cortex (10 Hz, 110% motor threshold, 15 min/session, 5 days/week), while HT consisted of 45-min gardening activities (e.g., planting, pruning, watering) conducted 5 days/week. Patients were evaluated using the Hamilton Depression Scale (HAMD), Hamilton Anxiety Scale (HAMA), and Stroke-Specific Quality of Life Scale (SS-QOL) before and after the 28-day intervention. Seventy-seven patients completed the trial, with three dropouts. All groups showed significant reductions in HAMD and HAMA scores post-treatment compared to baseline ($p<0.01$). Group D demonstrated a statistically significant improvement in SS-QOL scores ($p<0.01$), while other groups did not ($p>0.01$). No significant difference in HAMD scores was found between Groups B and C ($p=0.399$). These results suggest that combining rTMS and HT provides greater benefits in managing PSD compared to either intervention alone. No serious complications were reported. This study supports the integration of rTMS and HT as an effective adjunct to standard antidepressant therapy for PSD.

***Keywords:*** Horticultural therapy; Repetitive transcranial magnetic stimulation; Depression; Stroke; Stroke rehabilitation

## 1. Introduction

Post-stroke depression (PSD) is a common affective disorder that occurs following a stroke, characterized by physical symptoms, a depressed mood, psychomotor retardation, and loss of interest.[1] Stroke, a prevalent cardiovascular disease with high rates of disability and mortality, frequently results in motor impairments and neuropsychological disorders, including PSD, cognitive dysfunction, and language impairments.[2] Approximately one-third of stroke patients develop PSD, with its incidence peaking within 3 months to 1 year post-stroke, affecting over 50% of patients during this period.[3,4] PSD imposes a significant burden on patients, their families, and society. In China, the hospital-reported prevalence of PSD is estimated at 39.5%.[5]

Current treatments for PSD include psychological management, pharmacological therapies, traditional Chinese medicine (TCM), and physical therapies.[6] TCM treatments – such as Wuling capsules,[7] flavored Banxia-Houpu decoction,[8] and Chaihu Shugan San[9] – combined with acupuncture and other external techniques, have shown promising efficacy with fewer adverse effects. Physical therapies, including exercise therapy, hyperbaric oxygen therapy, and repetitive transcranial magnetic stimulation (rTMS), are also utilized; however, these methods are often associated with high costs, inconsistent efficacy, and potential adverse effects. As a result, non-pharmacological interventions like horticultural therapy (HT) have gained increasing attention in recent years.

rTMS is a non-invasive neural stimulation technique that uses pulsed magnetic fields to modulate the activity of the central nervous system.[10] It has been shown to promote neural network reconstruction, stimulate neural progenitor cell differentiation and proliferation, and alleviate depression symptoms. On the other hand, HT involves engagement with plants and natural environments to reduce stress and improve mental well-being.[11] Studies have indicated that HT can effectively alleviate depressive symptoms, making it a valuable therapy for PSD.[12] According to the Chinese Expert Consensus on the Clinical Practice of Post-Stroke Depression,[13] HT is not currently included as a recommended intervention; however, its use has expanded rapidly in recent years, with an increasing number of hospitals exploring HT as a treatment for PSD. This study aims to combine HT with rTMS to develop a non-invasive, cost-effective, and replicable treatment approach for PSD. By examining the potential synergistic effects of these therapies, we seek to provide innovative therapeutic options for managing PSD and improving patient outcomes. We hypothesize that, when administered alongside standard antidepressant, the combination of HT with rTMS will be more effective in treating PSD than rTMS or gardening therapy alone. To test this hypothesis, we propose a 28-day double-blind, randomized controlled trial (RCT), followed by a 6-month follow-up assessment, to evaluate the clinical efficacy of HT combined with rTMS in the treatment of PSD and compare outcomes across the different intervention groups.

## 2. Study design

This study was a double-blind RCT conducted at the Department of Rehabilitation Medicine, Guangxi International Zhuang Medicine Hospital (The Affiliated Hospital of Guangxi University of Traditional Chinese Medicine, a tertiary care hospital) in Nanning, Guangxi, China, from March 2024 to December 2024. Ethical approval was obtained from the Guangxi International Zhuang Medicine Hospital Institutional Review Board (approval number: 2022-042-01), and the trial was registered with the China Clinical Trials Registry (registration number: MR-45-23-041506).

### 2.1. Participants

#### *2.1.1. Diagnostic criteria*

Participants were diagnosed with PSD according to the Chinese Expert Consensus on Clinical Practice of Post-Stroke Depression. Depressive symptoms were observed within 1 month – 2 years after stroke onset. Diagnosis was supported by the Hamilton Depression Scale (HAMD),[14] Hamilton Anxiety Scale (HAMA),[15] and Stroke-Specific Quality of Life Scale (SS-QOL).[16]

#### *2.1.2. Inclusion criteria*

Participants were eligible if they met the following criteria: (i) Fulfilled the diagnostic criteria for PSD; (ii) aged between 30 and 75 years; (iii) had stable vital signs, were conscious, and demonstrated good compliance; (iv) had a HAMD score ≥7; (v) had not received antidepressant or other treatments that could affect the study results within 2 weeks before enrollment; and (vi) provided informed consent, signed by the patient or their legal guardian.

#### *2.1.3. Exclusion criteria*

Participants were excluded if they met any of the following conditions: (i) Had a history of psychiatric disorders; (ii) had significant dysfunction of other vital organs; (iii) were diagnosed with malignancies such as tumors; (iv) had metallic or ferromagnetic implants; (v) had severe consciousness disorders, coma, aphasia, cognitive impairment, or deafness affecting communication; (vi) refused to participate in the study; (vii) had hearing impairments; (viii) had a history of epilepsy.

### 2.2. Sample size calculation

Sample size was calculated based on the study by Simning *et al.*[17] The primary outcome variables were HAMD, HAMA, and SS-QOL scores. The sample size was determined as 5 – 10 times the number of items in the scales, with an additional 10% to account for potential dropouts. To achieve 80% power at a 0.05 significance level, 18 participants were required per group. Considering the 10% dropout rate, the final sample size was set at 20 participants per group, totaling 80 participants.

### 2.3. Randomization

Eighty PSD patients were recruited and randomly assigned into four treatment groups using a computer-generated randomization sequence (http://randomization.com) with a block size of four. Group assignments were sealed in numbered envelopes and disclosed to participants after baseline testing. To ensure allocation concealment, the envelopes remained sealed until the intervention assignment and were opened by the study coordinator only after baseline assessments were completed. The allocation process to the intervention group was carried out by social workers. Following group assignment, participants, occupational therapists, and outcome assessors remained blinded to group allocation. Data analysts, who were not involved in the study design or clinical implementation, also remained blinded to group assignments.

### 2.4. Intervention

All participants received daily antidepressant medication (escitalopram, 10 mg/day) and standard rehabilitation treatment provided by the medical staff of the rehabilitation department. The specific interventions for each group were as follows (Figure 1): Group A (control group): Antidepressant medication only; Group B: Antidepressant medication combined with rTMS. rTMS was administered for 15 min/session, 5 days/week, targeting the left dorsolateral prefrontal cortex[18] Stimulation parameters included an intensity of 110% of the motor threshold and a frequency of 10 Hz; Group C: antidepressant medication combined with HT. HT sessions lasted 45 min, 5 days/week. Activities were conducted in groups of 3 – 4 patients under the guidance of occupational therapists and social workers. Tasks were assigned based on the patient's functional ability, ranging from fine motor activities (e.g., pruning plants) to auxiliary tasks (e.g., stabilizing tools or providing assistance). The therapist adjusted the interactive mode in real-time according to the patient's performance, offering assistive devices or facilitating cooperation as needed. Social workers supervised the sessions and provided gardening knowledge to enhance participants' self-recognition of the intervention. This approach integrates functional rehabilitation with psychological support and is personalized according to the degree of patients' dysfunction and treatment stage; Group D: antidepressant medication combined with both rTMS and HT. Both interventions were applied as described above. The HT program was designed based on the scale of rehabilitation therapy hall. This intervention phase lasted 28 days, followed by a 6-month follow-up evaluation.

### 2.5. Outcome measurements

Clinical outcomes were assessed using HAMD,[14] HAMA,[15] and SS-QOL scales.[16] Assessments were conducted at baseline (pre-treatment) and on the 28$^{th}$ day of treatment (post-treatment).

HAMD: Consists of 17 items, each scored from 0 to 2 or 0 to 4, with a total score ranging from 0 to 50. Higher scores indicate more severe depressive symptoms. The HAMD evaluates a range of depressive disorders, including those associated with physical illnesses, providing a comprehensive measure of depression severity.

HAMA: Includes 14 items, each scored from 0 to 4, with a total score ranging from 0 to 56. Higher scores indicate greater anxiety severity. The HAMA comprehensively assesses anxiety, including somatic symptoms.

Stroke-Specific Quality-of-Life Scale: designed to evaluate quality of life in stroke patients. Each item is scored from 0 to 5, with higher scores indicating a greater impact on quality of life. SS-QOL is used in clinical settings to assess the effectiveness of rehabilitation measures and adjust treatment plans accordingly. Outcome assessments were conducted by an occupational therapist who was blinded to the intervention assignments.

### 2.6. Statistical methods

Baseline characteristics for all four treatment groups were analyzed using descriptive statistics and reported as numbers, percentages, means, and standard deviations. Mixed-effects restricted maximum likelihood regression was used to compare mean differences in HAMD, HAMA, and SS-QOL scores among the four treatment groups on day 28 and during the 6-month follow-up. Assuming a non-adherence and dropout rate of 20 – 30%, a sample size of 20 participants per group was determined. A 95% confidence interval that did not cross zero was considered statistically significant.

## 3. Results

A total of 294 participants who met the inclusion criteria were invited to participate in this community-based intervention study. Of these, 132 individuals (44.9%) consented to take part in the trial. Eighty

patients who completed pre-intervention assessments and randomization were enrolled and assigned to one of four treatment groups. In Group A (control group), 19 participants (95.0%) completed the post-intervention assessment; one participant dropped out due to transportation issues. In Group B (classical therapy group: rTMS group), all 20 participants (100.0%) completed the post-intervention assessment. In Group C (HT group), 19 participants (95.0%) completed the assessment, while one participant withdrew due to transportation issues. In Group D (combined therapy group), 19 participants (95.0%) completed the assessment, while one participant withdrew to sensitivity to the smell of soil during garden activities. Participants who dropped out were excluded from the final analysis (Figure 1 for the trial process).

Baseline demographic and clinical characteristics – including age, gender, height, weight, education level, underlying diseases, and disease duration – were comparable across the four treatment groups, with no statistical significant differences (Table 1).

Changes in primary outcome measures among participants who completed the 28-day intervention are presented in Table 2. Below is a breakdown of results for each scale and treatment group.

At baseline, Group D (combined HT and rTMS group) had slightly higher mean HAMD scores compared to Group A (control group), with values of 24.50 (standard deviation [SD] = 1.54) and 23.94 (SD = 1.89), respectively. After treatment, mean HAMD scores decreased significantly across all groups ($p<0.01$). The post-treatment mean scores were 16.44 (SD = 1.46) for Group B (rTMS group), 17.11 (SD = 3.12) for Group C (HT group), and 19.78 (SD = 2.49) for Group A.

There were no significant differences in baseline HAMA scores among the four treatment groups. Baseline means were: Group A, 26.65 (SD = 1.15); Group B, 26.00 (SD = 1.70); Group C, 25.89 (SD = 0.90); and Group D, 25.67 (SD = 1.14). Following the intervention, all groups showed a significant decrease in mean HAMA scores compared to baseline ($p<0.01$), as shown in Table 2.

Meanwhile, Group D (combined HT and rTMS group) exhibited slightly higher baseline SS-QOL scores (43.26, SD = 11.62) compared to Group A (41.97, SD = 12.54). After 28 days of treatment, the SS-QOL scores were 44.84

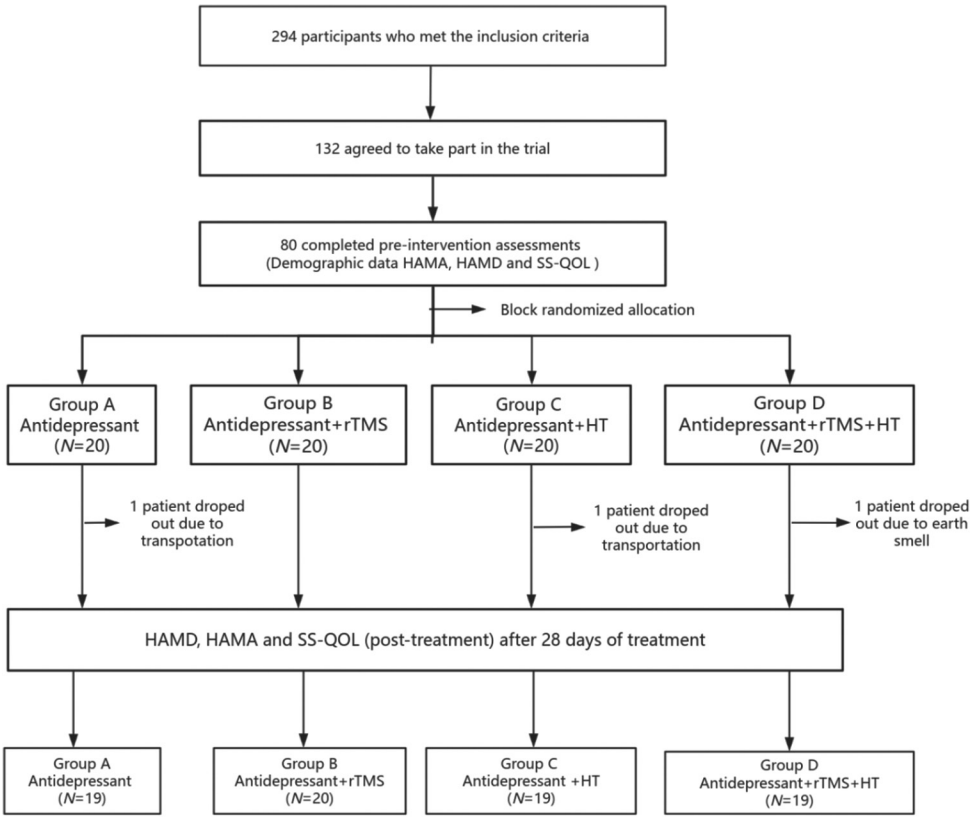



**Figure 1.** Trial profile
Abbreviations: HAMA: Hamilton Anxiety Scale; HAMD: Hamilton Depression Scale; HT: Horticultural therapy; SS-QOL: Stroke-Specific Quality of Life Scale; rTMS: Repetitive transcranial magnetic stimulation.

**Table 1. Demographic data of the patients**

| Characteristics | Group A (*N*=20) | Group B (*N*=20) | Group C (*N*=20) | Group D (*N*=20) |
|---|---|---|---|---|
| Age, years | 64.1 (5.6) | 68.2 (5.2) | 65.2 (5.5) | 69.2 (5.8) |
| Female, *n* (%) | 9 (45) | 8 (40.0) | 9 (45) | 9 (45) |
| Height, cm | 159.7 (9.2) | 156.0 (8.6) | 152.4 (9.1) | 153.5 (10.3) |
| Weight, kg | 54.4 (11.8) | 52.9 (12.4) | 60.3 (11.1) | 56.6 (8.2) |
| Medical history, *n* (%) of hypertension | 12 (60.0) | 14 (70.0) | 13 (65.0) | 15 (75.0) |
| Medical history, *n* (%) of diabetes mellitus | 7 (35.0) | 9 (45.0) | 7 (35.0) | 7 (35.0) |
| Education, years | 11.8 (2.5) | 12.0 (2.3) | 11.4 (2.6) | 11.7 (2.4) |
| Disease duration, months | 6.9 (1.85) | 5.0 (2.06) | 7.9 (2.07) | 4.8 (1.90) |

Note: Data are expressed as mean (standard deviation) unless otherwise specified.
Abbreviation: no.: Number.

**Table 2. Comparison and analysis of outcomes**

| Group | Statistical parameter | HAMD score | HAMA score | SS-QOL score |
|---|---|---|---|---|
| A (*N*=19) | Baseline | 23.94 (1.89) | 26.50 (1.15) | 41.97 (12.54) |
| | Post-intervention | 19.78 (2.49) | 23.33 (2.00) | 42.82 (9.75) |
| | *t* | 9.873 | 6.174 | 2.543 |
| | *p* | <0.01 | <0.01 | 0.417 |
| B (*N*=20) | Baseline | 24.78 (1.06) | 26.11 (1.71) | 42.34 (11.36) |
| | Post-intervention | 16.44 (1.46) | 19.33 (2.35) | 44.84 (10.63) |
| | *t* | 18.513 | 9.981 | 3.687 |
| | *p* | <0.01 | <0.01 | 0.638 |
| C (*N*=19) | Baseline | 24.67 (1.46) | 25.89 (0.90) | 40.76 (9.48) |
| | Post-intervention | 17.11 (3.12) | 21.00 (1.75) | 45.59 (10.75) |
| | *t* | 9.628 | 10.238 | 4.568 |
| | *p* | <0.01 | <0.01 | 0.434 |
| D (*N*=19) | Baseline | 24.50 (1.54) | 25.67 (1.14) | 43.26 (11.62) |
| | Post-intervention | 14.44 (2.04) | 17.39 (2.66) | 59.28 (9.82) |
| | *t* | 17.009 | 14.966 | -8.785 |
| | *p* | <0.01 | <0.01 | <0.01 |

Notes: Data are expressed as mean (standard deviation). Significance was set at $p<0.05$ compared to baseline.
Abbreviations: HAMA: Hamilton Anxiety Scale; HAMD: Hamilton Depression Scale; SS-QOL: Stroke-Specific Quality of Life Scale.

(SD = 10.63) for Group B, 45.59 (SD = 10.75) for Group C, and 42.82 (SD = 9.75) for Group A. While Group D showed a statistically significant improvement in quality of life ($p<0.01$), no significant differences were found among the other groups ($p>0.05$). These results are detailed in Table 2.

Participants also reported improvements in secondary outcomes such as cognition, sleep, appetite/weight, mental health, and sexual function scores after treatment. These improvements persisted 1 month after the intervention.

Table 3 presents a comparison of efficacy between groups post-treatment. There were no significant group differences between Group B (rTMS group) and Group C (HT group) based on HAMD scores ($p=0.399$). However, significant between-group differences were observed in comparisons involving other groups ($p<0.05$). Analysis of HAMA scores revealed statistically significant differences among all four treatment groups ($p<0.05$).

Figure 2 illustrates the mean changes in HAMD, HAMA, and SS-QOL at pre-treatment and post-treatment (28 days) across the four treatment groups. Both HAMD and HAMA scores showed statistically significant reductions in all groups following the intervention ($p<0.01$). In contrast, only Group D exhibited a statistically significant increase in SS-QOL scores ($p<0.01$), while the other groups demonstrated minimal changes pre- and post-intervention.

## 4. Discussion

This study demonstrated significant improvements in anxiety and depression among all enrolled participants. Post-intervention analysis revealed that Groups B, C, and D achieved significantly better outcomes than Group A, with Group D (combined HT and rTMS) showing the most pronounced improvements. Analysis of HAMA scores indicated that Group B (rTMS alone) outperformed Group C (HT alone). However, no statistically significant difference in HAMD scores was found between these two groups. These findings are detailed in Table 3. The most effective treatment outcome was achieved with the combination of antidepressants, rTMS, and HT (Group D), followed by the antidepressant and rTMS group (Group B), and the antidepressant and HT group (Group C), respectively.

**Table 3. Post-intervention comparison between all groups**

| Outcome | Group 1 | Group 2 | AD | *p* |
|---|---|---|---|---|
| HAMD score (post-intervention) | A (19.78±2.49) | B (16.44±1.46) | 3.333 | <0.01 |
| | A (19.78±2.49) | C (17.11±3.12) | 2.667 | <0.01 |
| | A (19.78±2.49) | D (14.44±2.04) | 5.333 | <0.01 |
| | B (16.44±1.46) | C (17.11±3.12) | −0.667 | 0.399 |
| | B (16.44±1.46) | D (14.44±2.04) | 2 | 0.013 |
| | C (17.11±3.12) | D (14.44±2.04) | 2.667 | <0.01 |
| HAMA score (post-intervention) | A (23.33±2.00) | B (19.33±2.35) | 4 | <0.01 |
| | A (23.33±2.00) | C (21.00±1.75) | 2.333 | <0.01 |
| | A (23.33±2.00) | D (17.39±2.66) | 5.944 | <0.01 |
| | B (19.33±2.35) | C (21.00±1.75) | −1.667 | 0.027 |
| | B (19.33±2.35) | D (17.39±2.66) | 1.944 | 0.011 |
| | C (21.00±1.75) | D (17.39±2.66) | 3.611 | <0.01 |

Notes: Data are expressed as AVG±SD. Significance was set at $p<0.05$ compared to each group.
Abbreviations: AVG: Average; AD: Standard deviation; HAMA: Hamilton Anxiety Scale; HAMD: Hamilton Depression Scale.

Reduced levels of peripheral and central brain-derived neurotrophic factor (BDNF) have been consistently observed in individuals with depression, including those with PSD.[19-23] BDNF plays a critical role in neuroplasticity, neuronal survival, and synaptic connectivity – all of which are compromised in depressive disorders. rTMS has been shown to upregulate BDNF expression, potentially helping reverse these neurobiological deficits. In addition, glutamate has emerged as another key biomarker for treatment response, with increased radiolabeled activity observed in the dorsolateral prefrontal cortex following rTMS stimulation.[24] This suggests that rTMS plays a role in modulating excitatory neurotransmission, which is often disrupted in depression.

Furthermore, rTMS has been associated with increased dopamine concentrations[25-27] and enhanced functional activity in neural networks involved in mood regulation, as demonstrated by functional imaging studies.[28] These changes may contribute to the alleviation of depressive symptoms by restoring balance within disrupted neural circuits. However, the precise mechanisms by which rTMS exerts its therapeutic effects remain an area of active investigation. A deeper understanding of these pathways could provide insights into the pathophysiology of PSD and aid in identifying novel therapeutic targets.

Accelerated rTMS protocols have been successfully employed in other populations, such as individuals with treatment-resistant depression and alcohol withdrawal cravings.[29-32] In addition, studies have explored the use of rTMS in acute stroke care for managing complications unrelated to depression.[33-36] Despite these advances, similar paradigms have not been widely applied in PSD populations. In this study, patients in Groups B and D received rTMS treatment at a frequency of 10 Hz for 15 min/session, administered 5 days/week for 4 weeks. This protocol demonstrated significant efficacy in reducing

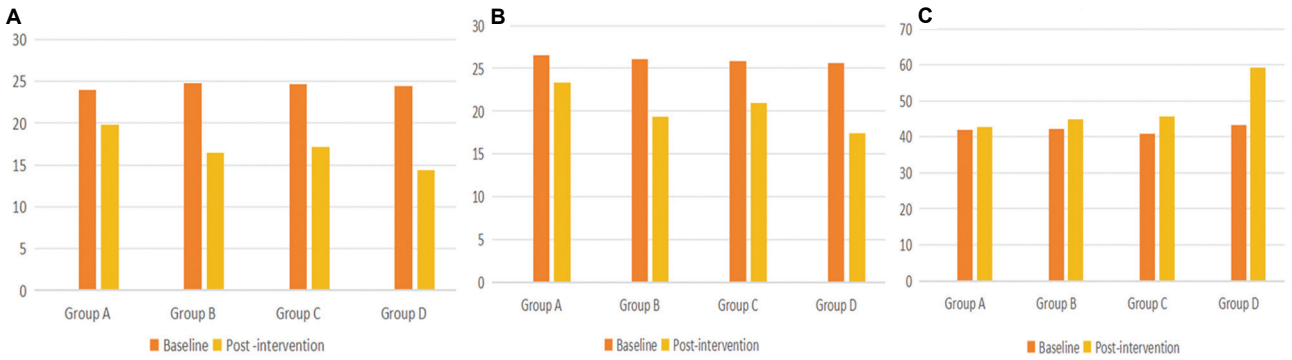



**Figure 2.** Changes in primary outcome measures. (A) HAMD score. (B) HAMA score. (C) SS-QOL score.
Abbreviations: HAMA: Hamilton Anxiety Scale; HAMD: Hamilton Depression Scale; SS-QOL: Stroke-Specific Quality of Life Scale.

depressive and anxiety symptoms, particularly when combined with HT. Regarding the primary objectives of our study, we found that following the intensive daily treatment, immediate results indicated a significant improvement in depressive symptoms among PSD patients treated with rTMS combined with HT. Previous studies have shown that mindfulness-based stress reduction combined with low intensity transcranial electrical stimulation effectively enhances psychological comfort and well-being.[33] Although these studies primarily focused on patients with generalized anxiety disorder, and the heterogeneity of mindfulness-based interventions introduces some limitations to drawing definitive conclusions, this growing body of research supports the benefits of combining rTMS with non-pharmacological therapies to improve quality of life.[34-37] Taylor *et al.*[38] have suggested that rTMS can alleviate depressive symptoms safely. Building on this, our future research will further explore the neural mechanisms underlying rTMS in combination with mindfulness-based stress reduction. Our current findings suggest that HT may help sustain the effects of rTMS, offering a more potentially durable treatment approach for PSD patients.

In our study, patients in Group B received rTMS at a frequency of 10 Hz for 15 min/session, administered 5 days/week for 4 weeks. This protocol aligns with the standard high-frequency rTMS protocols commonly used in the treatment of depression. Previous studies have demonstrated that high-frequency stimulation of the dorsolateral prefrontal cortex is effective in modulating neural circuits associated with mood regulation and improving depressive symptoms.[18] For instance, O'Reardon *et al.*[39] used a similar protocol of 10 Hz stimulation for 4 – 6 weeks in patients with major depressive disorder and reported significant clinical improvements. Similarly, Berlim *et al.*[40] conducted a meta-analysis of rTMS studies and found that high-frequency stimulation protocols ranging from 10 Hz to 20 Hz were associated with robust antidepressant effects. Moreover, variations in rTMS dosing parameters, such as session duration, frequency, and total number of sessions, can influence treatment outcomes. For example, Fitzgerald *et al.*[41] demonstrated that longer session duration and higher total pulses per session (e.g., 20 min of stimulation) may lead to more pronounced symptom improvements in treatment-resistant depression. Compared to these studies, our protocol utilized a relatively moderate session duration (15 min) and treatment period (4 weeks), which may explain the relatively rapid onset of symptom relief observed. Furthermore, Li *et al.*[42] noted that rTMS mainly plays a short-term role in post-stroke aphasics. Longer-term and large-scale studies are essential to explore the effect of rTMS with different frequencies on post-stroke aphasia. By integrating HT with rTMS, our study aimed to explore whether the combined therapy could shorten the overall treatment duration. However, due to a high dropout rate during follow-up, we currently lack sufficient data to confirm this effect. Nonetheless, preliminary observations indicate that most patients continued to show improvement, which will be an important focus of our future research.

While previous studies have primarily focused on the use of rTMS as a standalone treatment for depression or PSD, our findings highlight the added value of combining rTMS with HT. This combination appears to address not only the neural dysfunction underlying PSD but also the psychological and behavioral aspects of recovery, contributing to a more holistic improvement in patients' health-related quality of life. Moreover, the sustained effects observed in our study, in contrast to Li *et al.*'s[42] findings of diminishing rTMS effects, suggest that the combined treatment with HT may play a critical role in maintaining the therapeutic gains achieved with rTMS.

Although our rTMS dosing protocol aligns with established guidelines, the integration of HT represents a novel therapeutic approach that warrants further exploration. Future studies should investigate the neural mechanisms underlying this combination therapy and assess whether variations in rTMS dosing parameters could further optimize treatment outcomes in PSD patients. rTMS remains one of the most precise methods for controlling the frequency and location of brain stimulation, offering distinct advantages over other therapeutic approaches.[43] Our data supports the hypothesis that rTMS is a safe and viable option to treat PSD symptoms. In addition to rTMS, HT has also been shown to improve depression in patients with PSD. However, the results of studies on HT vary significantly due to numerous factors, including the time elapsed from the onset of the stroke to the initiation of treatment, the severity of depression, the dose, and the specific protocol of HT employed.[43,44] These variables can substantially influence the effectiveness of HT in the treatment of depression. The severity of depression is a particularly strong predictor of response to therapy.[45] In our study, the severity of depression was assessed using the HAMD score. The mean baseline HAMD score of the intervention groups was 24.5, which is classified as severe depression. This high baseline severity likely influenced the outcomes observed in our study. Notably, our results did not show the superiority of HT over rTMS in terms of effectiveness.

On the other hand, a study[32] reported that high-frequency rTMS treatment over 2 weeks was effective in treatment-resistant major depressive disorder and may serve as an effective alternative or adjunctive therapy for

patients suffering from PSD. Future RCTs are needed to optimize the accelerated rTMS protocol and validate these preliminary findings. As observed in our study, patients with PSD often require more intensive or multimodal interventions. Food and Drug Administration-approved rTMS offers a viable adjunctive therapy for major depression.[46] Furthermore, the "Clinical Application and Operational Standards of Repetitive Transcranial Magnetic Stimulation" outlined in the Shanghai Expert Consensus (2022) highlights the positive and safe effects of rTMS in the treatment of stroke-related conditions, including PSD. These endorsements further promote the utility of rTMS as a future therapy for PSD.

Our study utilized a stimulation frequency and dosing protocol of rTMS that likely promoted the release of neurotransmitters such as serotonin and BDNF in the cerebral cortex. These mechanisms are believed to improve local cerebral blood flow and regulate gene expression related to neuronal excitability, thereby alleviating depressive symptoms.[23] These findings align with those of Shen *et al.*,[47] who conducted a systematic review and meta-analysis on RCTs and concluded that rTMS is both effective and safe for the treatment of PSD.

Previous studies, such as Berlim *et al.*,[40] have explored similar high-frequency protocols for depression, with session duration ranging from 15 to 20 min and treatment periods extending up to 6 weeks. These studies consistently demonstrated significant improvements in depressive symptoms, supporting the efficacy of high-frequency rTMS. In addition, Li *et al.*[42] reported that the effects of rTMS intervention were mainly plays a short-term role statistically significant. We have observed statistically significant results over a 28-day clinical trial period. Next, we will consider extending the treatment period up to 6 weeks to investigate whether rTMS, when combined with other interventions such as HT, would sustain its therapeutic potential and long-term benefits.

Several limitations were identified in this study. First, the small sample size and single-center design limit the generalizability and statistical power to demonstrate the superiority of rTMS combined with HT over other treatment groups. Larger, multicenter studies are needed to better evaluate the comparative effectiveness of this combination therapy. Second, participants in this study exhibited heterogeneous clinical features, including variations in the time from stroke onset, the type of depression, and the severity of depressive symptoms. While this heterogeneity reflects real-world clinical practice, it also limits the universality of the results to broader populations. Third, the assessment tools used in this study may not be sensitive enough to detect subtle differences between the four treatment groups. Future studies would benefit from incorporating more precise and validated instruments to better capture the nuanced effects of different treatment modalities. Finally, the study did not present the data for the follow-up period. The 28-day treatment duration may have been sufficient to detect immediate therapeutic effects, but a longer-term follow-up study could provide deeper insights into the durability of the treatment benefits and potentially reveal a greater degree of improvement over time.

## 5. Conclusion and future perspectives

This study provides sufficient evidence to support the use of rTMS combined with HT as a promising treatment option for PSD. The combination therapy demonstrated additional improvements in depressive symptoms beyond those observed with standard therapy alone. These findings highlight the potential of integrating rTMS with HT to enhance recovery in patients with PSD. However, further research with larger sample sizes, more sensitive assessment tools, and extended follow-up periods is needed to validate these results and optimize treatment protocols. Therefore, future studies should focus on optimizing synergistic strategies for non-drug treatment, including identifying the optimal combination of rTMS parameters (e.g., frequency, stimulation site) and HT types. Further clinical validation is required. Our study is expected to contribute to the development of a safer and more comprehensive rehabilitation program by minimizing side effects while maximizing the treatment efficacy.

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## Conflict of interest

The authors declare no conflicts of interest.

## Author contributions

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## Ethics approval and consent to participate

Ethics approval for the study was granted by the Research Ethics Committee of Guangxi International Zhuang Medicine Hospital (approval number: 2022-042-01), and the trial was registered under the China Clinical Trials Registry (MR-45-23-041506). Consent has been obtained from participants to take part in the study before commencement.

## Consent for publication

Written informed consent was obtained from all participants for participation and publication of participants' data. All data were published under strict protection of patient privacy, and ensuring no identifying information was exposed or disclosed.

## Availability of data

The data that support the findings of this study are available on request from the first author and corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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