Integrative medicine rehabilitation for post-stroke limb spasticity: A multicenter randomized controlled trial

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Research Article

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Abstract

Objective: This study aimed to determine whether integrative medicine rehabilitation (IMR) that combines conventional rehabilitation (CR) with Tui Na and traditional Chinese external medicine Baimai-ruangao is more effective than CR alone for the treatment of post-stroke limb spasticity.

Design: Multicenter randomized controlled intervention trial involving 16 hospitals across ten cities in China.

Subject: 444 patients with post-stroke limb spasticity were randomly assigned to IMR group (n=222) or CR group (n=222).

Methods: Tui Na was performed for patients with post-stroke limb spasticity. Traditional Chinese external medicine Baimai-ruangao as the massage medium was applied on the skin surface. The treatment course was 1 month. Muscle tone in the spastic muscles (elbow flexors, wrist flexors, finger flexors, knee extensors, ankle plantar flexors) was evaluated using the Modified Ashworth Scale (MAS), and the primary endpoint was the change in MAS score from baseline to 4 weeks.

Results: The IMR group showed a significantly better reduction in the MAS scores for five muscle groups than the CR group after the 4-week intervention. Improvements were sustained at the 3-month and 6-month follow-up. Patients with a baseline muscle tone score of 1+ to 4 on the MAS for the affected limb showed the greatest benefit of IMR. No adverse reaction was observed in the IMR group.

Conclusion: The combination of CR and IMR is safe and more effective than CR alone for alleviating post-stroke limb spasticity.

Introduction

An estimated 1.5-2.0 million cases of stroke occur annually in China\(^1\). The rapidly increasing number of stroke patients poses a formidable challenge to China's healthcare system. Stroke rehabilitation has developed rapidly in China since the 2000s, and stroke rehabilitation units are still evolving to adopt a more standardized form of care. Integrative medicine is increasingly being accepted around the world, combining complementary therapies such as traditional Chinese medicine (TCM) and conventional allopathic interventions. With the development of integrative medicine, more stroke rehabilitation centers in China are utilizing TCM, such as acupuncture, Chinese herbal medicine, diet, massage, and exercise, to adapt to the demands of an increasing patient population. A comprehensive strategy, termed integrative medicine rehabilitation (IMR), incorporates TCM therapies along with conventional rehabilitation (CR).

Traditional Chinese therapeutic massage, Tui Na, and traditional Chinese external herbal medicine are commonly applied in IMR for the treatment of post-stroke limb spasticity. Tui Na is a non-invasive intervention that is widely applied to treat post-stroke complications including limb spasticity in China\(^2-5\). A systematic review suggested that Tui Na may be effective in the treatment of post-stroke limb
spasticity with no significant side effects\(^{(2)}\). However, cases that are suitable for Tui Na are not clearly specified in the Guidelines for post-stroke rehabilitation in China.

The traditional Chinese external medicine *Baimai-ruangao*, which was first recorded in Clinic notes of Tibetan medicine by *Gongmangongquebanda* in the 16\(^{th}\) century, was listed in the National Drug Catalogue for Basic Medical Insurance in 2000 and was the first external medicine approved by the State Drug Administration of China for stroke therapy. It has also been shown to have neuroprotective and anti-spasticity effects in stroke patients\(^{(6,7)}\). However, most of the published studies only investigated the effects of Tui Na or *Baimai-ruangao* alone, and whether the combination of these treatments has a better effect on post-stroke limb spasticity is still unknown.

We conducted a large, multicenter, randomized controlled trial across 16 centers in China. In this trial, we designed prescriptions of Tui Na and *Baimai-ruangao* for stroke in China according to the advice of TCM experts at five high-level traditional medicine universities, to be recommended as a standard treatment for post-stroke limb spasticity. Three of the five universities are Double First-Class Universities, including Shanghai Traditional Medicine University, Nanjing Traditional Medicine University, and Guangdong Traditional Medicine University. With a holistic view of the human body, we conducted a combined treatment of Tui Na and traditional Chinese external medicine *Baimai-ruangao* to balance the *Qi* and blood of the body, and to promote alterations in tendon compliance and physiological changes in muscle fibers\(^{(8-10)}\). This study aimed to determine whether IMR (which combines CR with Tui Na and traditional Chinese external medicine *Baimai-ruangao*) is more effective than conventional rehabilitation for relieving post-stroke limb spasticity.

**Methods**

*Study design*

This clinical trial was conducted in accordance with the Declaration of Helsinki at 16 hospitals in 10 large cities, and was registered at ClinicalTrials.gov \(http://clinicaltrials.gov/\) (Registration no. NCT03054974). This study was approved by the respective institutional review boards and ethics committees, and complied with the regulatory requirements. Participants were recruited by poster advertisements in the hospitals and surrounding communities. All participants were provided study participation informative document as well as detailed counseling about the study objectives and procedures. Subsequently, only those who provided written informed consent for participation were enrolled in the study.

*Study population*

Participants who had a definitive diagnosis of stroke, according to the World Health Organization definition\(^{(11)}\) and confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) examination were included if they qualified the following criteria: 1) age range, 18–75 years; 2) patients
who experienced stroke in the preceding 1–12 months; 3) Mini-mental State Examination (MMSE) score\(^{(12)}\) of \(\geq 16\); and 4) presence of spasticity of at least one muscle group with a Modified Ashworth Scale (MAS) score\(^{(13)}\) for the limbs of \(\geq 1\). The exclusion criteria were: patients with serious heart, liver, kidney, hematopoietic system-related diseases, cancer, or serious psychiatric disorders; history of receiving anti-spasticity drugs (e.g., oral medication, intrathecal baclofen, botulinum toxin, and nerve blocks) or surgical interventions; pregnant women; history of receiving TCM treatment in the preceding 3 months; participation in any other clinical trial within the preceding 6 months; inability to receive Tui Na or traditional Chinese external medicine Baimai-ruangao due to severe musculoskeletal conditions (e.g., fracture, amputation, severe arthritis, joint contracture, complex regional pain syndrome, or serious skin damage).

**Randomization and blinding**

Eligible patients were randomly assigned to receive either CR or IMR at a 1:1 ratio using a computer-generated randomization list. The details of the allocation sequence were concealed in sequentially numbered, opaque, sealed, and stapled envelopes. Cardboard was placed inside the envelope to block the passage of intense light. The allocation sequence was concealed from the researchers who enrolled and assessed the participants. The envelopes were opened only at the time of intervention allocation after the enrolled participants had completed all baseline assessments.

All participants were treated separately to prevent inter-participant communication. Prior to enrolment, patients were informed that they had an equal chance of allocation to the experimental or control group. While participants allocated to the groups were aware of the allocated arm, the outcome assessors and statistical analysts were blinded to the group identity.

**Intervention protocols**

Both groups received conventional stroke rehabilitation treatment once per day, 5 days per week for the 4-week study period. To examine the impact of IMR on the treatment group, the CR therapy was applied in a similar fashion in both groups. Rehabilitation treatments were conducted by certified rehabilitation therapists with more than 5 years of experience with stroke patients, and were specifically trained according to the investigator’s brochure. Study interventions were developed according to the Chinese stroke rehabilitation treatment guidelines. Each session included physical therapy (PT) and occupational therapy (OT). A 2-hour session of PT training involved traditional rehabilitation treatments (including proper positioning and exercises, muscle stretching, range of motion [ROM] exercises, and muscle strengthening exercises), neuromuscular facilitation techniques, and antagonistic muscle electrical stimulation therapy. A 30-min session of OT training was conducted according to the patient’s ability to carry out activities of daily living (ADL), including manual simulation operation, sports, and entertainment training. In addition, the IMR group received a 40-min session of Tui Na therapy as a bedside treatment in the supine position (5 times each week for a total of 4 weeks) and anointment with Baimai-ruangao before each Tui Na therapy session.
**Tui Na treatment.** Tui Na program was performed by certified massage therapists with 5–10 years of clinical experience. A 40-min session of Tui Na was performed according to specific methods established by experts with rich theoretical and practical experience in Chinese massage and used in a previous study\(^{(14)}\). The Tui Na manipulation methods are shown in Supplementary Table 1. After Tui Na, patients should feel mild-to-moderate soreness and distension\(^{(14)}\).

**Traditional Chinese external medicine Baimai-ruangao.** Baimai-ruangao (Z20043178, QiZheng Tibetan medicine) is made from herbs including Turmeric, Nutmeg, Spikenard, Actinolite, Radix Glycyrrhizae, Artificial musk, Rhizoma Zingiberis, Caraway, Rhizoma Acori Calami, Zanthoxylum and Tronae\(^{(15} 16)\). Baimai-ruangao was used as the massage medium and was applied to the skin surface at a dose of 5 g/limb for each session.

**Outcome measurements**

The primary outcome was MAS score. Muscle tone was selected as the primary outcome measure for easy comparison of the results with those of previous studies. The secondary outcome was the Fugl–Meyer Assessment (FMA) motor scale\(^{(17)}\) for assessment of motor dysfunction. All outcomes were evaluated at five time-points: week 0 (baseline), week 2 (midway of the intervention period), week 4 (after treatment), week 16 (follow-up), and week 28 (follow-up). Adverse events were recorded on a case report form for evaluation of their relationship with the study intervention.

**Statistical analysis**

Sample size calculations were based on previous studies and detailed in our previous papers\(^{(18-20)}\). All analyses were conducted by a statistician at the Nanjing Medical University using statistical software SPSS 17.0. Student’s t-test and the rank sum test were used to compare the differences in the values of outcome measures (baseline minus follow-up) between the two groups. Subgroup analyses stratified by baseline MAS score were conducted. \(P\) values less than 0.05 was considered indicative of statistical significance.

**Results**

We recruited participants from ten large cities via advertisements by posters in communities and hospitals. Approximately 558 evaluations yielded the desired sample size of 444 participants. Of the 137 subjects who dropped out, 98 were lost to follow-up in the two groups and 39 failed to complete the treatment. In total, 152 subjects in the IMR group and 155 subjects in the CR group completed all the treatments and measurements. Figure 1 shows the trial flow diagram.

**Baseline characteristics**

There were no significant between-group differences with respect to the baseline demographic characteristics. Our baseline results are described elsewhere\(^{(16)}\).
Primary and secondary endpoints

Primary outcome

There were significant between-group differences with respect to the mean changes in the MAS scores (from baseline to week 4) for the elbow flexors ($P=0.0422$), the wrist flexors ($P=0.0022$), the finger flexors ($P=0.0175$), the knee extensors ($P=0.0215$), and the ankle plantar flexors ($P=0.0205$). The relief of spasticity in the IMR group was better than that in the CR group, and the benefit was maintained until 3 and 6 months after the last intervention in the elbow flexors ($P<0.0001$, $P<0.0001$), the wrist flexors ($P=0.0001$, $P=0.0002$), the finger flexors ($P=0.0001$, $P<0.0001$), the knee extensors ($P=0.0029$, $P=0.0364$), and the ankle plantar flexors ($P=0.0195$, $P=0.0016$) (Table 1, Figure 2).

Secondary outcomes

FMA. Significant differences were noted in FMA scores between the two groups (from baseline to week 4, $P=0.0012$). The superiority of IMR over CR was maintained at 3 and 6 months after the last intervention (3 months: $P=0.0001$; 6 months: $P=0.0018$) (Table 2, Figure 2).

Subgroup analysis. We divided the IMR group into 3 subgroups based on the baseline MAS scores. In the subgroup 1* (MAS score 0-1), significant differences were found in the MAS-elbow flexors scores ($P=0.0241$), MAS-wrist flexors scores ($P=0.0246$), MAS-finger flexors scores ($P=0.0246$), and MAS-knee extensors scores ($P=0.0451$) between baseline and after 4 weeks of treatment in the IMR group. In the subgroup 2* (MAS score 1+-2), significant differences were found in MAS-elbow flexors scores ($P<0.0001$), MAS-wrist flexors scores ($P<0.0001$), MAS-finger flexors scores ($P<0.0001$), and MAS-knee extensors scores ($P<0.0001$), and MAS-ankle plantar flexors scores ($P<0.0001$). In the subgroup 3* (MAS score 3-4), the differences in MAS-elbow flexors scores ($P=0.0025$), MAS-finger flexors scores ($P=0.0062$), and MAS-ankle plantar flexors scores ($P=0.0010$) achieved statistical significance after the last intervention (Table 3).

Safety. The adverse events occurring in this study were recorded on a case report form after evaluating their relationships with the study intervention. Fortunately, no adverse events occurred in this study.

Discussion

This multicenter trial showed that IMR had better effects than CR alone for relieving post-stroke limb spasticity. The beneficial results on limb spasticity were sustained during the follow-up period. The main outcome was spasticity as measured by the MAS. This scale has been considered the “gold standard” for measuring muscle tone\(^{(13)}\).

The FMA scale, the most common measure of motor recovery in stroke patients, was used for measuring the motor function of limbs in this study\(^{(17)}\). After 4 weeks of treatment, the improvement in the FAM scores in the IMR group was significantly greater than that in the CR group. The significant improvement
in FMA scores for limb motor function after 4 weeks of CR combined with Tui Na and traditional Chinese external medicine Baimai-ruangao treatment was maintained for 3 and 6 months, compared with those of the CR group. These findings suggest that the reduction in the degree of limb spasticity may greatly contribute to the improvement in limb motor function.

No treatment-related adverse reaction was observed among the IMR-treated patients. Tui Na is simple, non-invasive, and easy to implement. As long as a licensed Tui Na therapist performs the manipulation, Tui Na is usually a safe procedure. The traditional Chinese external medicine Baimai-ruangao is a classic prescription for external use. In the hands of experienced practitioners, the traditional Chinese external medicine Baimai-ruangao is very safe. These findings suggest that IMR is a safe and effective treatment that reduces the post-stroke spasticity of limb muscles and improves the motor function in the short-term (4 weeks) and long-term (6 months).

Furthermore, CR in combination with Tui Na and traditional Chinese external medicine Baimai-ruangao may have beneficial effects by improving muscle tone of the affected limb at different levels of spasticity. It was most advantageous for patients who had a baseline MAS score of 1+ to 2 for the muscles of the affected limb. Subgroup analysis suggested that the effect of CR in combination with Tui Na and traditional Chinese external medicine Baimai-ruangao on post-stroke limb spasticity was different at different stages of post-stroke recovery, and it was most advantageous for patients who had recent onset of stroke (disease duration: 1–3 months)\(^{(16)}\). Therefore, the combination of Tui Na and traditional Chinese external medicine Baimai-ruangao has potential as a preferred treatment for early rehabilitation of stroke patients with mild limb spasticity (MAS 1+ to 2).

To the best of our knowledge, the effect of Tui Na or traditional Chinese external medicine Baimai-ruangao on post-stroke limb spasticity has not been investigated in a large randomized controlled clinical trial. However, Tui Na or traditional Chinese external medicine Baimai-ruangao is commonly applied in stroke rehabilitation treatment. Thus, this kind of integrative approach is consistent with common clinical practice in China. Our study is the first large sample, randomized controlled trial of Tui Na to provide clinical evidence for the efficacy of Tui Na combined with traditional Chinese external medicine Baimai-ruangao for the treatment of post-stroke limb spasticity.

**Study Limitations**

Some limitations of our study should be acknowledged. During the trial, the therapists could not be blinded. We did not control for therapists’ expectations of the effectiveness of integrative therapy, which may have affected the effects of IMR. Another limitation was that sham Tui Na or placebo external medicine was not used as a control treatment. Thus, our results may be affected by a probable placebo bias.

**Conclusion**
In conclusion, IMR, a combination therapy including traditional remedy involving Tui Na and traditional Chinese external medicine *Baimai-ruangao*, was found to be more effective than CR alone in patients with post-stroke limb spasticity. Our trial demonstrated that treatment of post-stroke limb spasticity with the combination of Western medicine and TCM (including Tui Na and traditional Chinese external medicine) may improve the outcomes of stroke rehabilitation.

**Declarations**

**Ethical Approval**

This clinical trial was conducted in accordance with the Declaration of Helsinki at 16 hospitals and was registered at ClinicalTrials.gov ([http://clinicaltrials.gov/](http://clinicaltrials.gov/); identifier: NCT03054974).

**Competing interests**

The authors have declared that no competing interests exist.

**Authors' contributions**


**Funding**

The Ministry of Science and Technology of the People's Republic of China through the Twelfth Five-Year National Science and Technology Pillar Program (2013BAI10B04).

**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

**Disclosures**

None.

**References**


### Tables

#### Table 1 Comparison of ΔMAS scores between the two groups

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Between the 2 Groups P-value</th>
<th>Between the baseline and follow-up in the CR Group P-value</th>
<th>Between the baseline and follow-up in the IMR Group P-value</th>
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<tbody>
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<td>ΔMAS-Elbow flexors muscle</td>
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<td>Baseline-WK2</td>
<td>0.0202</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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<tr>
<td>Baseline-WK4</td>
<td>0.0422</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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<td>Baseline-MTH3</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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<tr>
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<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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<td>Baseline-MTH6</td>
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<td>0.0004</td>
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<td>ΔMAS-Knee extensors muscle</td>
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<td>ΔMAS-Ankle plantar flexors muscle</td>
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<td>0.0016</td>
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<td>&lt;0.0001</td>
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</table>

The data are presented as the mean ± standard deviation (SD) , 95%CI.
ΔChange in value before vs after treatment.

MAS=Modified Ashworth Scale; WK=week; MTH=month.

Table 2 Comparison of ΔFMA scores between the two groups

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Between 2 Groups (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Between the baseline and follow-up in the CR Group P-value</td>
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<td>0.0018</td>
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</tbody>
</table>

The data are presented as the mean ± standard deviation (SD), 95%CI.

ΔChange in value before vs after treatment.

FMA=Fugl-Meyer total score; MBI=Modified Barthel Index. WK=week; MTH=month

Table 3 Subgroup analysis of change in MAS score in the IMR Group (between the baseline and follow-up) according to the level of spasticity

<table>
<thead>
<tr>
<th>Level of spasticity</th>
<th>Elbow flexors muscle</th>
<th>Wrist flexors muscle</th>
<th>Finger flexors muscle</th>
<th>Knee extensors muscle</th>
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<td>Wk2</td>
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<tr>
<td>1*</td>
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<td>0.1583</td>
<td>0.0450</td>
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<td>0.3195</td>
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<tr>
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<tr>
<td>3*</td>
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<td>Wk4</td>
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<td>1*</td>
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<td></td>
</tr>
</tbody>
</table>

MAS, Modified Ashworth Scale; Wk, Week; MTH, Month.

The level of spasticity *: 1*, MAS score 0 or 1; 2*, MAS score 1+ or 2; 3*, MAS score 3 or 4.

: Sample size too small and statistical analysis could not be carried out.

Figures
Figure 1. Flow of participants through the trial.

**Figure 1**

Flow of participants through the trial.
Figure 2: Means of ΔMAS, ΔFMA at Four Testing Time Points. (a) ΔMAS-elbow flexors muscle for the IMR and CR at four testing time points (mean±SD). *P<0.05, **P<0.01, compared to CR group. (b) ΔMAS-wrist flexors muscle for the IMR and CR at four testing time points (mean±SD). **P<0.01, compared to CR group. (c) ΔMAS-finger flexors muscle for the IMR and CR at four testing time points (mean±SD). *P<0.05, **P<0.01, compared to CR group. (d) ΔMAS-knee extensors muscle for the IMR and CR at four testing time points (mean±SD). *P<0.05, **P<0.01, compared to CR group. (e) ΔMAS-ankle plantar flexors muscle for the IMR and CR at four testing time points (mean±SD). *P<0.05, **P<0.01, compared to CR group. (f) ΔFMA for the IMR and CR at four testing time points (mean±SD). **P<0.01, compared to CR group.

Figure 2
Mean ΔMAS and ΔFMA at four testing time-points.

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.
• SupplementaryTable1.docx