1. Abstract

1.1. Objective: We aimed to investigate the efficacy of integrating paired associative stimulation (PAS25) with low-temperature thermoplastic plate orthosis (LTTPO) to address post-stroke wrist flexor spasticity.

1.2. Methods: In this prospective randomized controlled study, 63 patients with post-stroke wrist flexor spasticity were recruited. Patients were assigned to receive either sham stimulation combined with LTTPO (control group, n = 31) or PAS25 combined with LTTPO (study group, n = 32) using a random number table. PAS25 was administered to the study group for 3 weeks, whereas the LTTPO was worn for approximately 4–6 h per day over 12 weeks. The primary outcome measured was Modified Ashworth Scale (MAS) scores, with visual analog scale (VAS), Fugl-Meyer Assessment (FMA), and swelling scale scores as secondary outcomes. Assessments were conducted at baseline, after 3 weeks of treatment, and at 4 and 8 weeks of follow-up.

1.3. Results: At the completion of treatment, the study group exhibited a significantly higher treatment effectiveness rate than the control group. The change in MAS at 3 weeks exhibited a significant disparity between the two groups (77.4% vs. 29%, p < 0.001). At the 4-week follow-up, significant changes were observed in MAS (96.9% vs. 45.2%, p < 0.001) and FMA scores (p = 0.007).

1.4. Conclusion: The integration of PAS with LTTPO proves to be an effective intervention for rapidly relieving wrist flexor spasticity post-stroke, with sustained effects observed at 8 weeks. Concurrently, the treatments improved active function but did not impact pain or swelling.

2. Introduction

Spasticity is a prevalent post-stroke symptom that can endure for varying durations. Studies have demonstrated that stroke patients commonly experience muscular spasticity [1]. Urban et al. have highlighted a higher incidence of spasticity in the upper limb than in the lower limb, with wrist flexor spasticity being particularly prevalent, accounting for 55%–75% of cases [2,3]. Wrist flexor spasticity plays a crucial role in limiting the recovery of fine motor function in the hand [4], presenting a substantial challenge in the rehabilitation field.

Studies have established that orthoses can effectively alleviate spasticity and are widely used in clinical settings. Among conventional orthoses, the low-temperature thermoplastic plate orthoses (LTTPOs) stand out [5]. While some evidence suggests that LTTPOs are beneficial in mitigating spasticity [6,7], their impact is relatively low, requiring prolonged wear to alter the viscoelasticity of peripheral muscles and soft tissue. Li et al. emphasize that motor function recovery is pivotal in spasticity relief [8]. Transcranial magnetic stimulation (TMS) is a noninvasive treatment modality extensively employed in stroke rehabilitation, particularly for addressing spasticity [9]. Peripheral neuromagnetic stimulation (PNS) presents an alternative for treating spasticity, urinary incontinence, swallowing difficulties, and pain through electrical stimulation applied to peripheral nerves or muscles [10].
Paired associative stimulation (PAS) [11] is a combined stimulation mode, leveraging physiological information from peripheral sensation in the sensory-motor feedback loop. This mode finely regulates central motor neurons and temporal-dependent plasticity mechanisms. Prior studies have demonstrated positive treatment outcomes in patients with post-stroke upper limb dysfunction who received TMS-assisted PNS to address spasticity [12]. However, limited information is available regarding PAS involving TMS combined with PNS. Therefore, this study investigates the effectiveness of PAS combined with LTTPO in managing wrist flexor spasticity among post-stroke patients.

3. Methods

3.1. Study Design

The study was conducted as a single-center, randomized controlled trial and received approval from the Ethics Committee of Shanghai Xuhui Central Hospital (reference no. 2022-144), participants and their relatives signed written informed consent for the study. The study was registered in the Chinese Clinical Trials Registry Platform (identifier: ChiCTR2300075497, Reg Date: 06/09/2023) and adheres to the Consolidated Standards of Reporting Trials (CONSORT) guidelines. A total of 63 patients came from the Department of Rehabilitation of Shanghai Xuhui Central Hospital, and study data were collected from January 2022 to June 2023.

3.2. Participants Criteria

Participants were recruited in four steps: (1) the patient’s attending physician, familiar with inclusion and exclusion criteria, screened potential participants and contacted the primary researcher; (2) the researcher explained the trial to potential participants; (3) participants were assessed for eligibility; and (4) participants and their relatives signed written informed consent.

The patients were divided into receiving false stimulation combined with LTTPO (control group) or PAS combined with LTTPO (study group). Participants were allocated using a unique computer-generated randomized table at a ratio of 1:1. The same assessors, who were blinded to the participants, dealt with all patients. All outcome assessors and care providers were different doctors. These individuals did not exchange information during implementation of the experiments, nor were they permitted to inquire about the subject of the intervention.

Inclusion criteria: (1) Patients aged 35–80 years old; (2) patients who had undergone treatment with alcohol and phenol block; (3) patients with previous wrist joint orthopedic surgery; (4) those with concurrent wrist extension spasticity grade II; (5) those with uncontrolled hypertension, diabetes, hyperlipidemia, arrhythmia, liver or kidney dysfunction; (6) patients with a history of epilepsy; (7) patients with severe mental disorders; (8) patients with malignant tumors; (9) patients with previous peripheral venous thrombosis.

3.3. Intervention

LTTPO: The patient’s maximum elbow extension range was measured. The orthosis was shaped by heating in 70°C water for 5 min, referencing 90% of the passive maximum range and covering the anterior and inferior 2/3 of the patient. During orthosis wear, a thick towel was wrapped around the upper limb on the affected side to prevent skin damage. The orthosis, when used for joint stabilization, was removed every 2 h throughout rehabilitation sessions to allow a 30-min relaxation period. The orthosis angle was adjusted weekly based on the patient’s condition. This regimen extended over 3 weeks.

PAS: The PAS mode of TMS treatment produced by Wuhan Yiruide Company (Model: YRD CCY-IV magnetic stimulator) was employed. The stimulator was placed at the M1 area on the affected side of the skull lesion. Before treatment, relevant information and possible adverse reactions were explained to the patient. The patient, positioned supine, had the magnetic stimulation coil fixed on the M1 area of the affected side, keeping the head still during treatment. PNS was applied to the median nerve in the wrist of the affected upper limb using a precise 8-shaped coil for the targeted area with a magnetic stimulation intensity of 120% motor threshold (MT). Electrical stimulation intensity caused slight contraction of the target muscle, with PNS followed by central stimulation and a time interval of 25 ms. A total of 90 stimulations were performed. The TMS treatment was administered over a course of fifteen sessions. Sham stimulation: All parameters and treatment intensities were identical to PNS, but the central coil was inverted, producing no effective magnetic stimulation. Peripheral nerve electrical stimulation did not emit impulses. Treatments were administered once daily, five times a week, for a total of 3 weeks. Patients wore orthotics for 4–6 hours a day for 12 weeks and paid attention to relaxing the wrist flexors.

3.4. Outcome Measures

The MAS was utilized for the assessment of spasticity. MAS ‘1’ and ‘1+’ were substituted by ‘1’ and ‘2,’ and ‘2’ and ‘3’ were substituted by ‘3’ and ‘4,’ respectively. The specific criteria were as follows [13]: (i) complete response (CR) if the original level degraded ≥2 or reduced to level 0; (ii) partial response (PR) if the original level degraded by 1; and (iii) no response (NR) if the original level did not change or upgraded.
Pain was assessed using the VAS [14] and swelling scale scores were assigned based on a 4-point scale. The FMA [15] was utilized to evaluate the degree of motor-function recovery after a stroke. All measurement indicators were assessed 24 h before treatment, at treatment completion, 4 weeks post-treatment, and 8 weeks post-treatment follow-up. The primary endpoint of the study was the change in MAS, with secondary endpoints encompassing comparisons of other treatment outcomes.

### 3.5. Statistical Analyses

Statistical analyses were conducted using SPSS Statistics. The Chi-squared test was used to assess changes in the clinical efficacy of MAS. Changes in primary and secondary indicators post-intervention among the groups were compared using Friedman analysis. The Wilcoxon rank-sum test served as the post hoc test. Repeated measures analysis of variance analyzed differences within groups. SPSS 22.0 software organized and statistically analyzed the data. Statistical descriptions of MAS scores were conducted based on the number of cases (%). For continuous variables meeting normal distribution and homogeneity of variance assumptions, independent-samples t-test was conducted. When not meeting the requirements of the parameter test, the Wilcoxon rank-sum test was used. A p-value less than 0.05 was considered a statistically significant difference.

### 4. Results

#### 4.1. Participant Inclusion

A total of 68 met the inclusion criteria, and 63 were included in the statistical analysis. Participant characteristics are summarized.

#### 4.2. Principal Outcome

The MAS change assessment. The scores were compared after 3-week interventions (T1–T0), and a significant difference was observed among the groups (p < 0.01). In the study group, CR was 31.1%, PR was 71.9%, and 25% achieved NR, resulting in an effective rate of 77.4%. 0% achieved CR, 29% achieved PR, and 71% achieved NR, with an effective rate of 29% in control group.

Following the 4-week follow-up (T2–T0), a significant difference was observed among the groups. In study group, CR was 21.9%, PR was 75%, and NR was 3.1%, with an effective rate of 96.9%. In control group, 0% achieved CR, 45.2% achieved PR, and 54.8% achieved NR, resulting in an effective rate of 45.2%.

A significant difference was noted among the groups following the 8-week follow-up (T3–T0) (p = 0.013). In the study group, 37.5% achieved CR, 59.4% achieved PR, and 3.1% achieved NR, with an effective rate of 96.9%. CR was 3.2%, PR was 71% and 25.8% achieved NR, resulting in an effective rate of 74.2% in control group.

#### 4.3. Secondary Outcomes

Comparison within groups revealed significant changes in all secondary indicators (p < 0.01) after 3 weeks of interventions, at 4 weeks follow-up, and at 8 weeks follow-up. Following 3-week interventions (T1–T0), between-group comparisons revealed significant differences in FMA (p < 0.001) and SS (p = 0.02).

Following 4-week follow-up (T2–T0), between-group comparisons indicated significant differences in FMA (p < 0.001). Similar results were obtained in between-group comparisons following the 8-week follow-up (T3–T0).

### 5. Discussion

In our study, we explored the effectiveness of the integration of PAS combined with LTTPO as an intervention for rapidly relieving wrist flexor spasticity post-stroke, with sustained effects over 8 weeks.

The observed increase in spasticity post-stroke can be attributed to alterations in neural properties [13]. Our use of the MAS to evaluate spasticity considers both muscle hypertonia from central nervous system damage and the viscoelasticity of soft tissues affected by a constant flexed position [14]. While MAS does not distinguish between whether the perceived muscle resistance of muscles is a result of reflex hyperexcitability, biomechanical changes, or both, its ease of administration and widespread clinical use, coupled with moderate to high intra-rater reliability for measuring wrist spasticity after stroke, makes it a valuable tool [15-17].

Our findings demonstrate a significant alleviation of MAS after 3 weeks of intervention in the study group, with sustained effects at the 4-week and 8-week follow-ups. In contrast, the control group exhibited a gradual increase in the effective rate of alleviating spasticity over time, suggesting a slower response to orthosis alone. This emphasizes the rapid and long-lasting effect of PAS25 combined with LTTPO in relieving wrist flexor spasticity post-stroke. Simultaneously, the motor function FMA also demonstrated significant improvement after 3 weeks of treatment, and this effect persisted during follow-up. This confirmed that PAS25 can improve the motor function of patients, which is consistent with previous research [18].

PAS emerges as a comprehensive stimulation mode grounded in the physiological interplay of peripheral sensation within the sensory-motor feedback loop. By finely regulating central motor neurons and temporal-dependent plasticity mechanisms, PAS orchestrates rapid, bi-directional neural function modulation in a few dozen cycles [11]. This stimulation technique involves the synchronized pairing of PNS with TMS, where PNS involves an electric stimulus on the median nerve and TMS constitutes a pulse over the primary motor cortex (M1). The inter-stimulus interval between these paired stimulations, specifically at 25 ms (PAS25) inducing long-term potentiation and 10 ms (PAS10) inducing long-term depression (LTD) in the cortex, contributes to the specificity and effectiveness of PAS [19]. Pandyan et al. [20] proposed a novel definition of spasticity, which aligns with the principles...
of PAS. Spasticity are characterized by intermittent or persistent involuntary muscle activation[20]. Notably, the recovery of motor function emerges as a pivotal factor in spasticity relief. PAS exhibits specificity in addressing this definition through its dual action. Firstly, it enhances the excitability of the affected cortex, fostering brain plasticity, ultimately relieving spasticity, and improving motor function, a trend consistently reported in previous research [21,22]. Secondly, PNS, operating as low-frequency electrical stimulation on peripheral nerves, projects to the center through afferent nerves and the spinal cord, promoting the reconstruction of brain function [23]. Simultaneously, the induced current circulates in the blood and lymphatic systems, enhancing the local blood supply to muscle groups and restoring muscle activity. The application of the excitatory co-stimulation mode PAS25 in our study, where electrical stimulation precedes magnetic stimulation, reinforces the belief that PAS25 effectively alleviates spasticity at both central and peripheral levels.

Our study observed a significant alleviation in the swelling score of the affected hand after 3 weeks of PAS25 treatment, coinciding with spasticity relief. This effect is likely linked to the improvement in the patient’s motor function, leading to reduced swelling. However, both groups exhibited a reduction in swelling over time, with no significant difference between them. Post-stroke swelling in the affected hand is influenced by various factors, including complications such as shoulder-hand syndrome [24]. The lack of improvement in the swelling score in this study, coupled with the absence of a notable difference between groups for wrist pain, suggests the potential influence of complications and the multifaceted nature of post-stroke swelling.

Revisions should be made to acknowledge certain limitations, despite the valuable insights gained from this study.

We should acknowledge some limitations of the study. The reliance on scales for most observation indicators highlights the need for future experiments to incorporate electrophysiological examinations and multimodal functional imaging technologies. Additionally, constraints related to the hospitalization period and local medical insurance policy influenced the intervention time and frequency. Finally, as a clinical study, the potential interference of other rehabilitation interventions cannot be entirely excluded, indicating a need for further exploration in future research efforts.

6. Conclusion
The integration of PAS combined with LTPTO is a suitable intervention for rapidly relieving wrist flexor spasticity after stroke. The treatment leads to lasting effects until 8 weeks. The treatment also improved active function, but did not affect pain or swelling.

7. Funding
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8. Ethical Approval
This study was implemented according to the Declaration of Helsinki, Good Clinical practice guidelines and the Consolidated Standards of Reporting Trials. This study was approved by the Ethics Committee of Shanghai Xuhui Central Hospital, Shanghai (reference no. 2022-144). Participants and their relatives signed written informed consent for the study.

Reference


