

Systematic Review

# The Efficacy and Safety of Different Noninvasive Therapies in the Treatment of Central Poststroke Pain (CPSP): A Network Meta-Analysis and Systematic Review

Li-Na Wu<sup>1</sup>, Hong-Yi Zheng<sup>2,3</sup>, Shi-Ao Xue<sup>2,3</sup>, Ke-Yu Chen<sup>4</sup>, Ruo-Yang Li<sup>3,5,\*</sup>

<sup>1</sup>Department of Rehabilitation Medicine, General Hospital of Xinjiang Military Region, 830002 Urumchi, Xinjiang, China

<sup>2</sup>School of Clinical Medicine, Southwest Medical University, 646099 Luzhou, Sichuan, China

<sup>3</sup>Department of Rehabilitation Medicine, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, 610072 Chengdu, Sichuan, China

<sup>4</sup>Department of Traditional Chinese Medicine, Chengdu Second People's Hospital, 610021 Chengdu, Sichuan, China

<sup>5</sup>School of Clinical Medicine, Hospital of Chengdu University of Traditional Chinese Medicine, 610032 Chengdu, Sichuan, China

\*Correspondence: [alis7718@outlook.com](mailto:alis7718@outlook.com) (Ruo-Yang Li)

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## Abstract

**Objective:** To evaluate the efficacy and safety of noninvasive therapies in the treatment of central poststroke pain (CPSP) by network meta-analysis and to provide an evidence-based basis for clinical practice. **Methods:** PubMed, Cochrane Library, EMBASE, CNKI, Wanfang, and VIP were searched for clinical randomized controlled studies on noninvasive therapy for CPSP. The retrieval time limit was from the establishment of each database to July 2022. The bias risk assessment tool recommended by Cochrane was used to evaluate the quality of the included randomized controlled trials (RCTs). Stata 14.0 was used for network meta-analysis, and Review Manager 5.3 software was used for traditional meta-analysis. **Results:** Twelve RCTs involving 8 treatment schemes and 641 patients were finally included. The results of the network meta-analysis showed the following rankings in visual analysis scale (VAS): super laser injury on stellate ganglia (SLI) > transcranial direct current stimulation (tDCS) > music therapy (MT) > repetitive transcranial magnetic stimulation (rTMS) > continuous theta burst stimulation (cTBS) > transcutaneous acupoint electrical stimulation (TAES) > common therapy (CT). The total clinical efficiency ranked as follows: psychological training of mindfulness (PT) > rTMS > CT. Clinical adverse reactions ranked as follows: rTMS > MT > CT > SLI. **Conclusions:** Noninvasive complementary therapy can effectively alleviate the pain of CPSP patients, and the efficacy and safety of SLI are relatively significant. However, due to the limitations of this study, the efficacy ranking cannot fully explain the advantages and disadvantages of clinical efficacy. In the future, more multicentre, large sample, double-blind clinical randomized controlled trials are needed to supplement and demonstrate the results of this study.

**Keywords:** noninvasive therapies; CPSP; Network meta-analysis; VAS

## 1. Introduction

Stroke is a common cerebrovascular disease with a high disability rate that mostly occurs in elderly individuals. Stroke is often accompanied by various sequelae, such as motor, swallowing, language and cognitive dysfunction. As one of the common sequelae of patients after stroke, central poststroke pain (CPSP) can have a very significant impact on the body, mind and daily life of patients. The pathogenesis of CPSP is not clear. Previous studies have suggested that CPSP is caused by thalamic damage, which results in thalamic pain. However, subsequent studies have shown that injuries in other parts outside the thalamus, such as the posterior limb of the internal capsule, the parietal cortex of the brain stem, the medulla oblongata, the insula, the tectum and other parts, can cause pain, and CPSP has a variety of clinical manifestations, including local, hemiplegia, and crossed pain and sensory abnormalities. Many studies have suggested that the pathogenesis of CPSP is complex [1–3].

At present, the treatment goal of CPSP is mainly to alleviate symptoms, which makes a complete cure difficult to achieve. Common therapies in the clinic include drug therapy and neuromodulation therapy. Depression drugs (amitriptyline and venlafaxine), anticonvulsant drugs (gabapentin, pregabalin, and lamotrigine) and glutamatergic drugs (ketamine) are common in drug therapy. The World Association for Neuroregulation defines “neuroregulation” as a biomedical engineering technology that uses invasive or noninvasive technology to change the activity of the central and peripheral nervous systems by means of electrical stimulation or drugs, thus improving symptoms and the quality of life of patients. Neuroregulation is an emerging discipline. Compared with the original damage and removal, it focuses on regulation; that is, the process is reversible, and the treatment parameters can be adjusted *in vitro* [4]. For some patients with strong drug resistance, invasive neuromodulation therapy is often used for treatment, such as invasive motor cortex (M1) stimulation



(MCS) [5] and deep brain stimulation (DBS) [6]. However, invasive neuromodulation therapy is more traumatic and expensive, and it easily causes postoperative neurological damage, making it difficult to apply in clinical practice. In recent years, many noninvasive complementary therapies have gradually appeared for the clinical treatment of CPSP, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). As the most commonly used noninvasive nerve regulation technology, rTMS and continuous theta burst stimulation (cTBS) use a changing magnetic field to generate an induction electric field in the cerebral cortex, thus regulating a series of physiological activities of neurons [7]. Unlike rTMS, tDCS mainly increases or decreases the excitability of neurons by inputting a weak constant direct current (DC) current into the brain, thus causing changes in brain function [8]. In addition, there are transcutaneous acupoint electrical stimulation (TAES) based on traditional Chinese medicine, super laser injury on stellate ganglia (SLI) based on laser irradiation principle and psychological therapy (like psychological training of mindfulness (PT) and music therapy (MT)). Some clinical studies [9] have confirmed their effectiveness, but the advantages and disadvantages of different noninvasive complementary therapies are rarely mentioned. Based on the frequency method of network meta-analysis, this study evaluates the clinical efficacy and safety of different noninvasive therapies in the treatment of CPSP with the visual analysis scale (VAS), clinical adverse reaction rate and total clinical effective rate as outcome indicators and ranks the related efficacy based on surface under the cumulative ranking (SUCRA).

## 2. Materials and Methods

### 2.1 Registration

This meta-analysis has been registered on PROSPERO, registration number CRD42022348055. PRISMA checklist is shown in **Supplementary Materials**.

### 2.2 Literature Search

The retrieval strategy adopted a combination of subject words and free words and adjusted the search words according to the search results. The retrieval time was from the establishment of the database to July 2022. The search databases were PubMed, Excellent Medica Database (EMBASE), Cochrane Library, CNKI, Wanfang, and VIP. The search terms included central poststroke pain, CPSP, central neurological pain after stroke, central neurological pain after cerebrovascular disease, central neurological pain after cerebral information, central neurological pain after intracerebral haemorrhage, and thalamic pain. See the appendix for all search formulas.

### 2.3 Study Selection

(1) The study was a randomized controlled trial (RCT). (2) The subjects were identified as stroke patients

by brain common therapy (CT), magnetic resonance imaging (MRI) and other imaging examinations and were diagnosed with CPSP with a pain score of 3 or more. (3) Treatment plan: The control group was treated with routine therapy (including routine rehabilitation training) combined with routine painkillers (gabapentin, pregabalin, and lamotrigine), and the treatment group was treated with noninvasive therapy based on routine rehabilitation training. (4) Outcome indicators: the main indicator was VAS, and the secondary indicators were clinical total effective rate and clinical adverse reaction rate.

### 2.4 Study Exclusion

(1) Unrelated literature, review, case reports, meta-analyses and other nonrandomized controlled trials; (2) Documents with repeatedly published data, incomplete data or unavailable data; (3) Repeatedly published literature in Chinese and English.

### 2.5 Data Extraction

Two researchers independently conducted literature screening and data extraction according to the inclusion and exclusion criteria and cross-checked the results. In case of disagreement, the third researcher participated in the discussion and decision. Endnote (Thomson ResearchSoft, Stanford, CT, USA) and Excel software (Microsoft, Redmond, WA, USA) were used for literature management and data extraction, mainly including the basic characteristics of cases included in the literature, intervention measures, course of treatment and outcome indicators. All continuous data are included in the difference before and after treatment (that is, the difference between indicators after treatment and before treatment). If the original text is not calculated, it will be calculated by itself. The formula is as follows:  $\text{corr}$  is usually taken as 0.5.

$$SD_{E,\text{change}} = \sqrt{SD_{E,\text{baseline}}^2 + SD_{E,\text{final}}^2 - (2 \times \text{Corr} \times SD_{E,\text{baseline}})}$$

$$\text{Mean}_{E,\text{change}} = \text{Mean}_{E,\text{final}} - \text{Mean}_{E,\text{baseline}}$$

### 2.6 Methodologic Quality

The quality of the included literature was evaluated according to the quality evaluation scale recommended in the Cochrane Handbook, including 6 parts: reporting bias, detection bias, performance bias, selection bias, loss of visit bias and other bias. Each part of the evaluation content can be judged as high, medium and low risk according to the standard.

### 2.7 Statistical Analysis

This study was based on the framework of frequency. For the continuity index, the mean difference (MD) was used as the effect quantity. If it was a binary variable, the odds ratio (OR) was used as the effect quantity, and the corresponding 95% confidence interval (CI) was calculated.

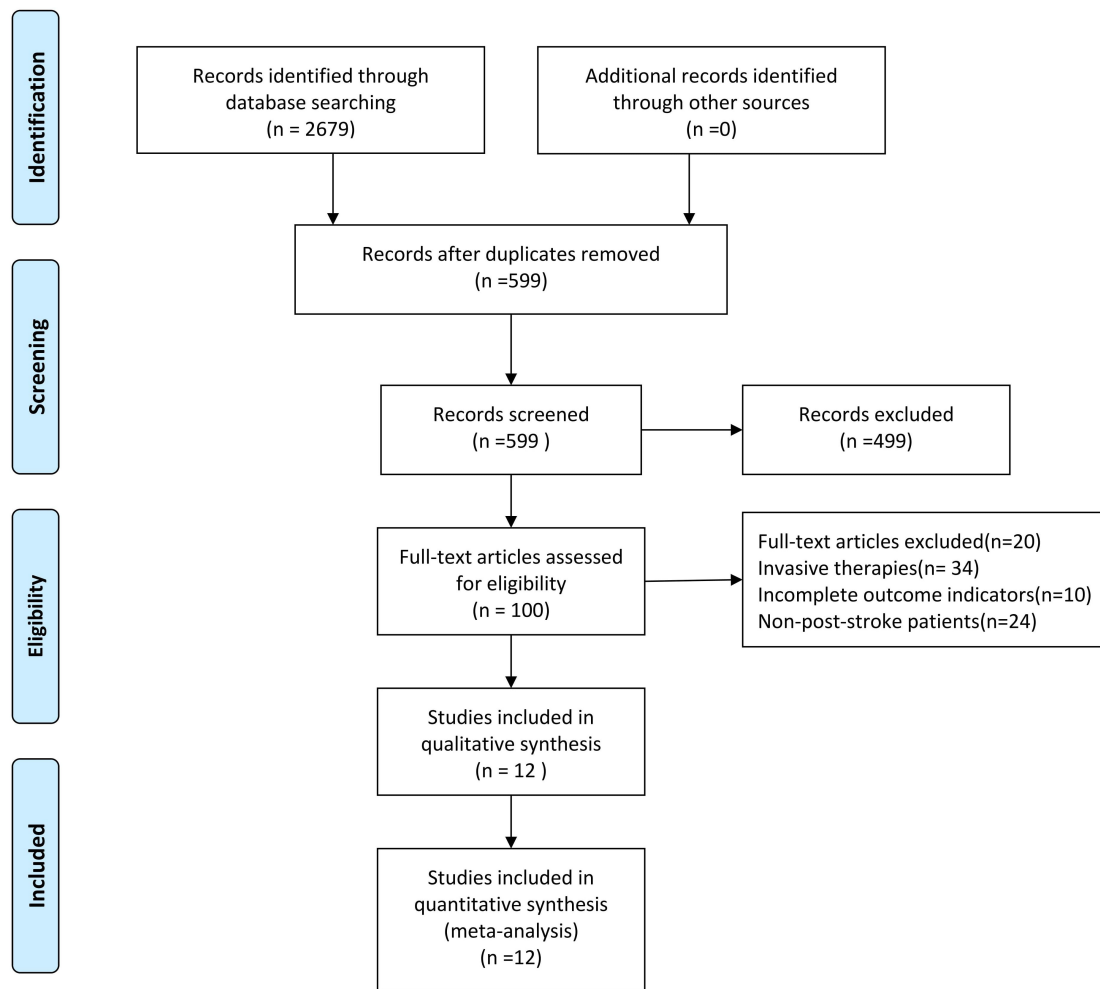


Fig. 1. Flow chart of literature screening.

culated. Stata 14.0 software (Stata Corporation, Lakeway, TX, USA) was used to draw a network evidence relationship diagram, forest diagram, grade probability diagram, funnel diagram and corresponding statistics. When testing the global consistency, if the difference was not statistically significant, that is,  $p > 0.05$ , no overall inconsistency existed [10]. If the study did not form a closed loop and the consistency test could not be carried out, Review Manager 5.3 software (the Cochrane Collaboration, Nordic Cochrane Center, Copenhagen, Denmark) was used for traditional meta-analysis. The heterogeneity test was mainly judged by  $I^2$ . If no heterogeneity existed between the research results ( $I^2 \leq 50\%$ ), the fixed effect model was used for meta-analysis; if heterogeneity existed among the research results ( $I^2 > 50\%$ ), the source of heterogeneity was further analysed, and the random effect model was used for meta-analysis. In this study, SUCRA was used to calculate the cumulative ranking probability of each treatment scheme. A larger SUCRA value, that is, a larger area under the curve of the cumulative probability ranking diagram, indicated a better effect of this intervention.

### 3. Results

A total of 2679 relevant studies were obtained in the initial examination, including 329 from CNKI, 680 from Wanfang, 178 from VIP, 597 from PubMed, 683 from EMBASE, and 212 from the Cochrane Library. They were imported into the software Endnote. After eliminating duplicate studies and strictly complying with the nanodischarge standard, 12 RCTs [8–19] were finally included, all of which were double-arm trials, with a total of 641 patients. Eight treatment schemes were involved, including common therapy (CT), SLI, MT, tDCS, TAES, rTMS, PT, and cTBS. The document screening process and results are shown in Fig. 1; the basic information of the included documents is shown in Table 1 (Ref. [11–22]).

#### 3.1 Risk of Bias

The included studies were evaluated using the Cochrane manual 5.1.0 bias risk assessment tool. In terms of the random allocation method, 9 studies were low risk, and the random number table method [11,13–17,20] was used for random allocation. Two studies were high risk [18,19] and did not mention randomization, and the remain-

**Table 1. Basic characteristics of the included trials.**

Author	Year	Number of patients		Age (year)		Male/female		Treatment		Intervention period	Outcome indicator
		I	C	I	C	I	C	I	C		
Zhou N [11]	2021	39	40	54.26 ± 6.47	51.85 ± 7.31	43/26		PT	CT	4W	VAS, total clinical effective rate
Chen JM [12]	2020	20	20	51.5 ± 17	55.1 ± 18.8	25/15		rTMS	CT	2W	VAS, clinical adverse reaction rate
Ou HN [13]	2015	29	30	59.78 ± 7.64	58.27 ± 5.03	33/26		TAES	CT	2W	VAS
Guo M [14]	2020	40	40	61.2 ± 2.3	59 ± 4.2	43/37		MT	CT	4W	clinical adverse reaction rate
He BJ [15]	2022	40	40	-	-	-		SLI	CT	2W	VAS, clinical adverse reaction rate
Sun W [16]	2019	20	20	48.1 ± 8.5	50.1 ± 7.9	27/13		rTMS	CT	4W	VAS, clinical adverse reaction rate
Duan Q [17]	2021	9	9	51 ± 7.8	49 ± 8.4	-		cTBS	CT	2W	VAS
Tan J [18]	2021	19	21	64.11 ± 7.52	66.24 ± 8.76	20/20		tDCS	CT	2W	VAS
Li N [19]	2016	37	33	58.3 ± 7.2	58.1 ± 7.4	35/35		rTMS	CT	4W	VAS, total clinical effective rate
Zhao YY [20]	2021	41	42	52.03 ± 14.22	52.11 ± 14.28	47/35		rTMS	CT	2W	VAS, total clinical effective rate
Bae SH [21]	2014	7	7	52.3 ± 2.8	51.1 ± 3.1	7/7		tDCS	CT	3W	VAS
Zhao CQ [22]	2021	19	19	49.55 ± 11.29		21/17		rTMS	CT	3W	clinical adverse reaction rate

I, intervention group; C, Control group; PT, psychological training; CT, common therapy; rTMS, repetitive transcranial magnetic stimulation; TAES, transcutaneous acupoint electrical stimulation; MT, music therapy; SLI, super laser injury; cTBS, continuous theta burst stimulation; tDCS, transcranial direct current stimulation; VAS, visual analysis scale.

ing studies only mentioned randomization without reporting specific random allocation methods. In terms of concealment of the random allocation scheme, one study [22] mentioned that allocation concealment was low risk, and the remaining the studies did not mention it. In terms of the blind method of the random allocation scheme, two studies [11,22] mentioned the use of the blind method, one of which was single-blinded [11] and the other double-blinded [12]. The measurement of outcome indicators was not mentioned in the literature. In terms of data integrity, the data included in the study were complete. In terms of selective reporting of research results, the included studies were all low risk. Other sources of bias were unclear. The risk assessment of bias in the included studies is shown in Fig. 2.

## 3.2 Visual Analysis Scale

### 3.2.1 Evidence Network of Visual Analysis Scale

Visual Analysis Scale (VAS) was reported in 10 studies involving 7 noninvasive treatment regimens. In the figure, the dot size represents the sample size of the intervention measure, and the line thickness represents the number of RCTs using the two treatment schemes. The seven treatments are all direct comparisons, and there is no closed-loop formation. The number of studies comparing rTMS with CT treatment was the largest (4 RCTs). The VAS evidence network is shown in Fig. 3A.

### 3.2.2 Publication Bias of Visual Analysis Scale

In this study, seven different treatment schemes were involved in the outcome indicators of VAS. Dots of different colours in the funnel chart represent the direct comparison between two different rehabilitation treatment schemes, and the number of dots represents the number of studies. Most of the dots in the funnel map of this study are symmetrically distributed on the vertical line and its two sides. Both sides

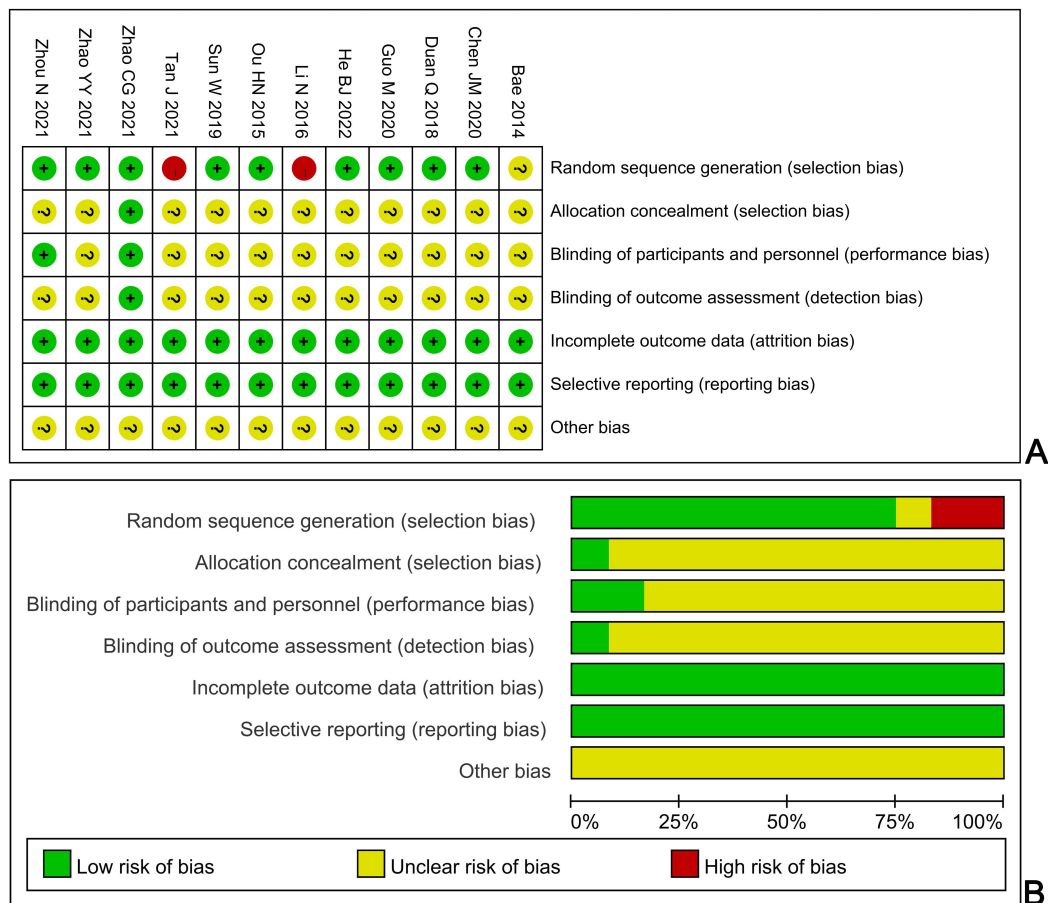
are essentially symmetrical, but a certain degree of publication bias may persist. See Fig. 3B for the funnel map.

### 3.2.3 Traditional Meta-Analysis of Visual Analysis Scale

For the same intervention measures, no obvious source of heterogeneity was found (tDCS vs. CT,  $I^2 = 67\%$ ), so the random effect model was used for meta-analysis. The remaining studies were essentially homogeneous ( $I^2 < 50\%$ ), and fixed effect models were used. Among the six noninvasive treatment schemes included, only the VAS difference between cTBS and CT was not statistically significant, and the decrease in the VAS of the other five noninvasive therapies after CPSP was significantly higher than that of CT ( $p < 0.05$ ), as shown in Table 2.

### 3.2.4 Network Meta-Analysis of Visual Analysis Scale

Seven treatment schemes were analysed by network meta-analysis, and 10 comparisons showed significant differences. The decreases in the VASs of continuous theta burst stimulation (cTBS) (MD = -1.33, 95% CI [-1.67, 0.99]), SLI (MD = -2.12, 95% CI [-2.70, -1.54]), TAES (MD = -0.89, 95% CI [-1.12, -0.66]), tDCS (MD = -1.84, 95% CI [-2.39, -1.28]), PT (MD = -1.70, 95% CI [-2.01, -1.39]) were significantly larger than that of CT; compared with rTMS, the decrease in VAS for SLI (MD = -0.79, 95% CI [-1.47, -0.12]) was larger than that for rTMS, and the decrease in VAS for TAES (MD = 0.44, 95% CI [0.03, 0.85]) was larger than that for rTMS. The decrease in VAS for TAES (MD = 1.23, 95% CI [0.61, 1.85]) was larger than that for SLI. Compared with TAES, tDCS (MD = -0.95, 95% CI [-1.55, -0.34]) and PT (MD = -0.81, 95% CI [-1.19, -0.43]) had larger VAS decreases. Other comparisons did not show significant differences, as shown in Fig. 3C.



**Fig. 2. Risk of bias graph.** (A) Risk of bias summary. (B) Risk of bias graph.

**Table 2. Traditional meta-analysis of VAS.**

Treatment	Numbers of RCTs	MD [95% CI]	I <sup>2</sup> /%	Z	p	Effect
rTMS vs. CT	4	-1.33 [-1.67, -0.99]	0	7.61	<0.00001	Fixed
cTBS vs. CT	1	-1.00 [-2.58, 0.58]	-	1.24	0.21	Fixed
SLI vs. CT	1	-2.12 [-2.70, -1.54]	-	7.16	<0.00001	Fixed
TAES vs. CT	1	-0.89 [-1.12, -0.66]	-	7.64	<0.00001	Fixed
tDCS vs. CT	2	-1.84 [-2.39, -1.28]	67	6.44	<0.00001	Random
PT vs. CT	1	-1.70 [-2.01, -1.39]	-	10.82	<0.00001	Fixed

Numbers of RCTs, The number of studies involving comparison of such interventions included; RCTs, randomized controlled trials; MD [95% CI], mean difference [95% confidence interval]; I<sup>2</sup>/%: heterogeneity; I<sup>2</sup>, I square; Z, z-value; p, p-value.

### 3.3 Total Clinical Effective Rate

#### 3.3.1 Evidence Network of the Total Clinical Effective Rate

Three studies reported the total clinical efficacy, including three noninvasive treatment regimens. The three treatments were all directly compared, and no closed loop formed. The number of studies comparing rTMS with CT treatment was the largest (2 RCTs). Few studies included this research index, and a traditional meta-analysis and funnel analysis consequently were not performed. The evidence network is shown in Fig. 4A.

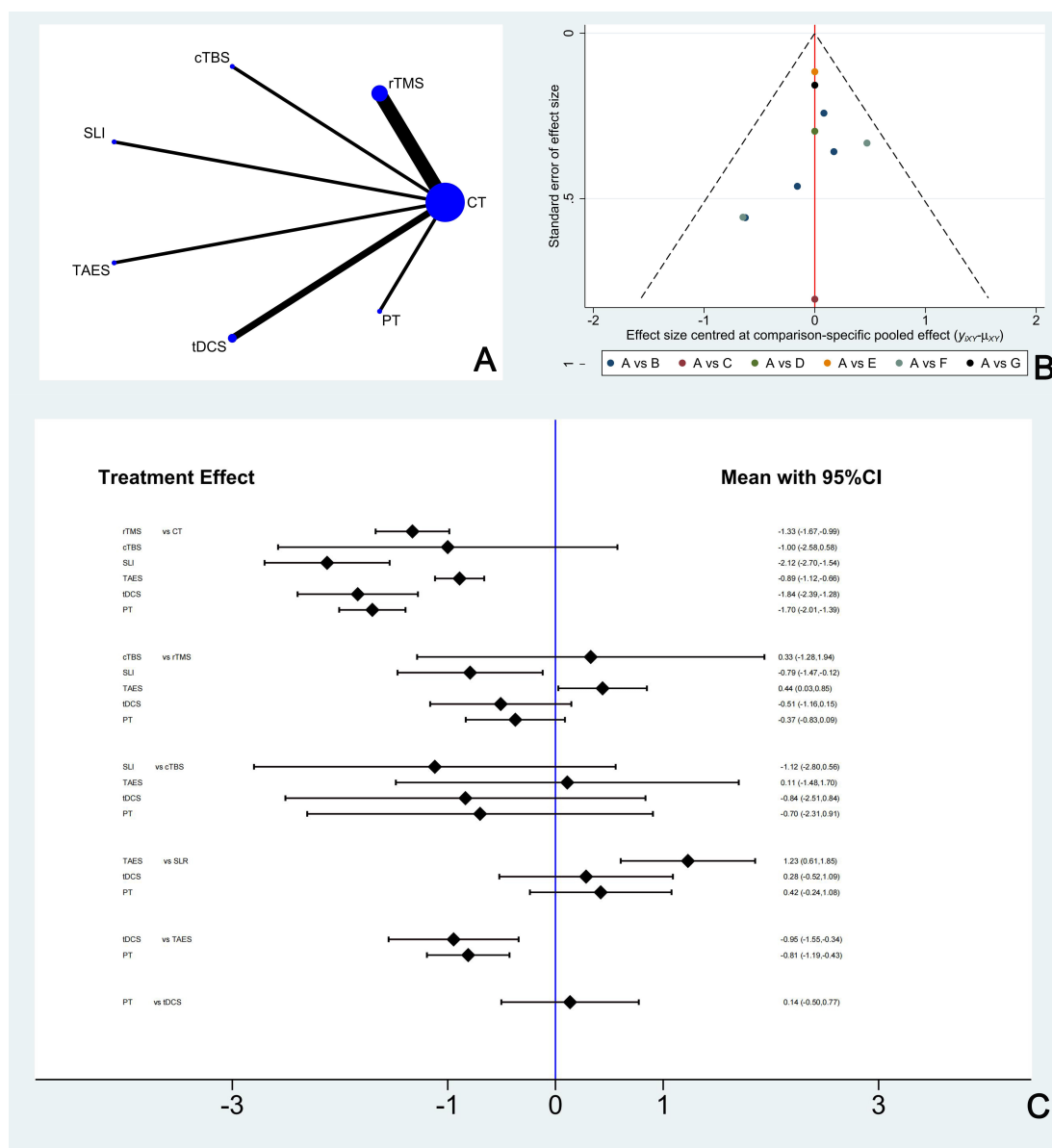
#### 3.3.2 Network Meta-Analysis of the Total Clinical Effective Rate

Three treatment schemes were analysed by network meta-analysis, and one comparison had a significant difference. Compared with CT, the total clinical effective rate of rTMS (OR = 2.73, 95% CI [1.38, 5.38]) was significantly higher than that of CT, and no significant difference was detected in other comparisons, as shown in Fig. 4B.

#### 3.4 Clinical Adverse Reaction Rate

Among all included studies, five studies [12,14–16, 22] reported adverse reactions, which were mainly mild ad-



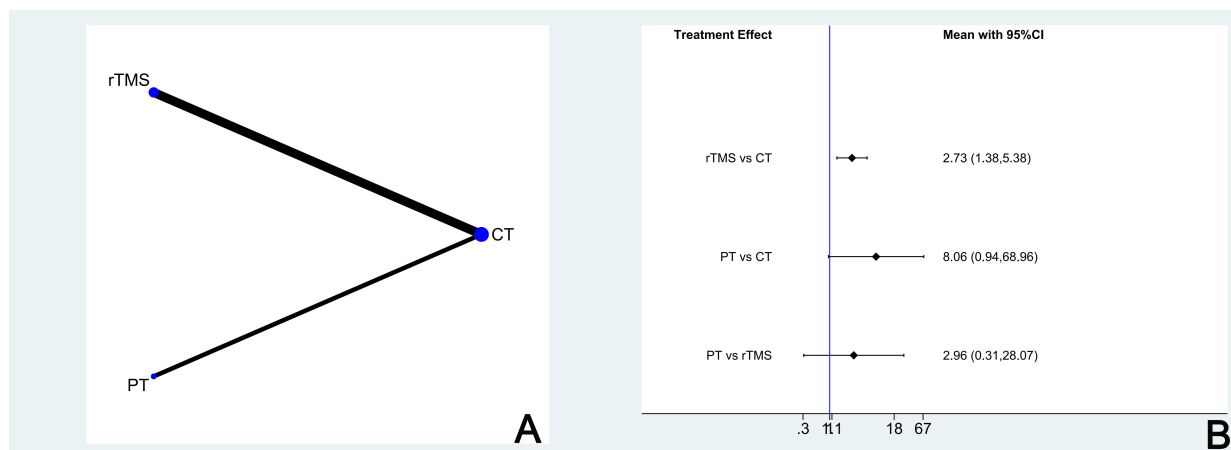


**Fig. 3. Relevant processing diagram of VAS.** (A) Network diagram of VAS scores. (B) Funnel diagram of FMA-UE scores. (C) Network meta-analysis of VAS scores. PT, psychological training; CT, common therapy; rTMS, repetitive transcranial magnetic stimulation; TAES, transcutaneous acupoint electrical stimulation; MT, music therapy; SLI, super laser injury; cTBS, continuous theta burst stimulation; tDCS, transcranial direct current stimulation; 95% CI, 95% confidence interval; VAS, visual analysis scale.

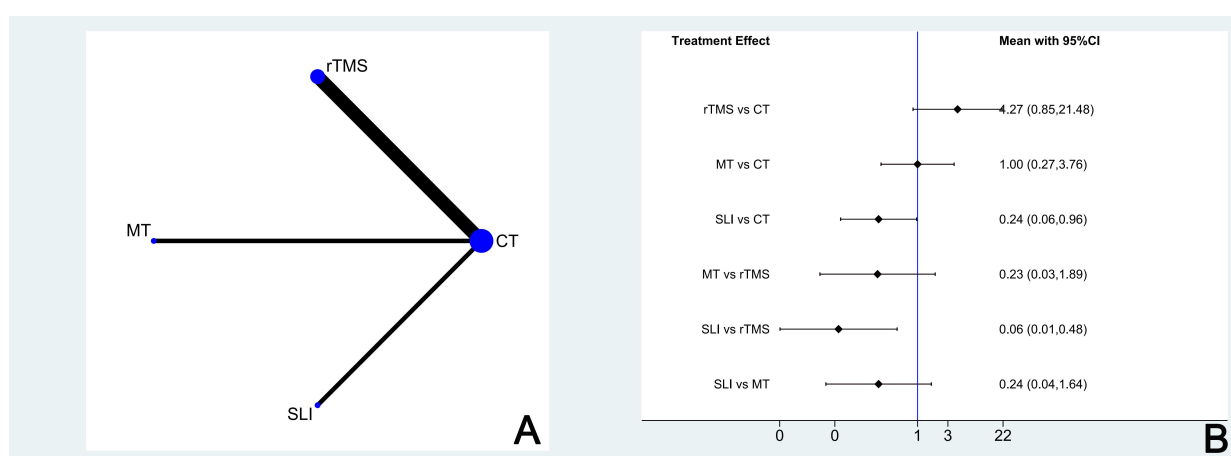
**Table 3. Adverse reactions/adverse events.**

Author	Treatment	I	C
Chen JM 2020 [12]	rTMS vs. CT	3 cases of mild headache	1 case of mild headache
Guo M 2020 [14]	MT vs. CT	2 cases of fatigue, 1 case of dizziness and 2 cases of lethargy	1 case of fatigue, 1 case of dizziness and 3 cases of lethargy
He BJ 2022 [15]	SLI vs. CT	1 case of sleepiness, 1 case of dry mouth, 1 case of dizziness	3 cases of sleepiness, 4 cases of dry mouth, 3 cases of dizziness
Sun W 2019 [16]	rTMS vs. CT	1 case of transient mild headache	None
Zhao CQ 2021 [22]	rTMS vs. CT	3 cases of short-term scalp numbness or facial muscle twitch	None

I, intervention group; C, Control group.



**Fig. 4. Relevant processing diagram of total clinical effective rate.** (A) Network diagram of the total clinical effective rate. (B) Network meta-analysis of the total clinical effective rate score.



**Fig. 5. Relevant processing diagram of clinical adverse reaction rate.** (A) Network diagram of the clinical adverse reaction rate. (B) Network meta-analysis of clinical adverse reaction rate.

verse reactions, such as mild headache, fatigue, dizziness, dizziness, drowsiness, dry mouth, temporary scalp numbness or facial muscle twitching. See Table 3 (ref. [12,14–16,22]) for the occurrence of adverse reactions/events.

#### 3.4.1 Evidence Network of the Clinical Adverse Reaction Rate

Five studies reported the clinical adverse reaction rate, including four noninvasive treatment regimens. All four treatments were directly compared, and no closed loop formed. The number of studies comparing rTMS with CT treatment was the largest (3 RCTs). Few studies included this research index, and traditional meta-analysis and funnel analysis were consequently not performed. The evidence network is shown in Fig. 5A.

#### 3.4.2 Network Meta-Analysis of Clinical Adverse Reaction Rate

The three treatment schemes were analysed by network meta-analysis, and the two comparisons had signif-

icant differences. The clinical adverse reaction rate of SLI (OR = 0.24, 95% CI [0.06, 0.96]) was significantly lower than that of CT. The clinical adverse reaction rate of SLI (OR = 0.06, 95% CI [0.01, 0.48]) was significantly lower than that of rTMS. No significant difference was detected in other comparisons, as shown in Fig. 5B.

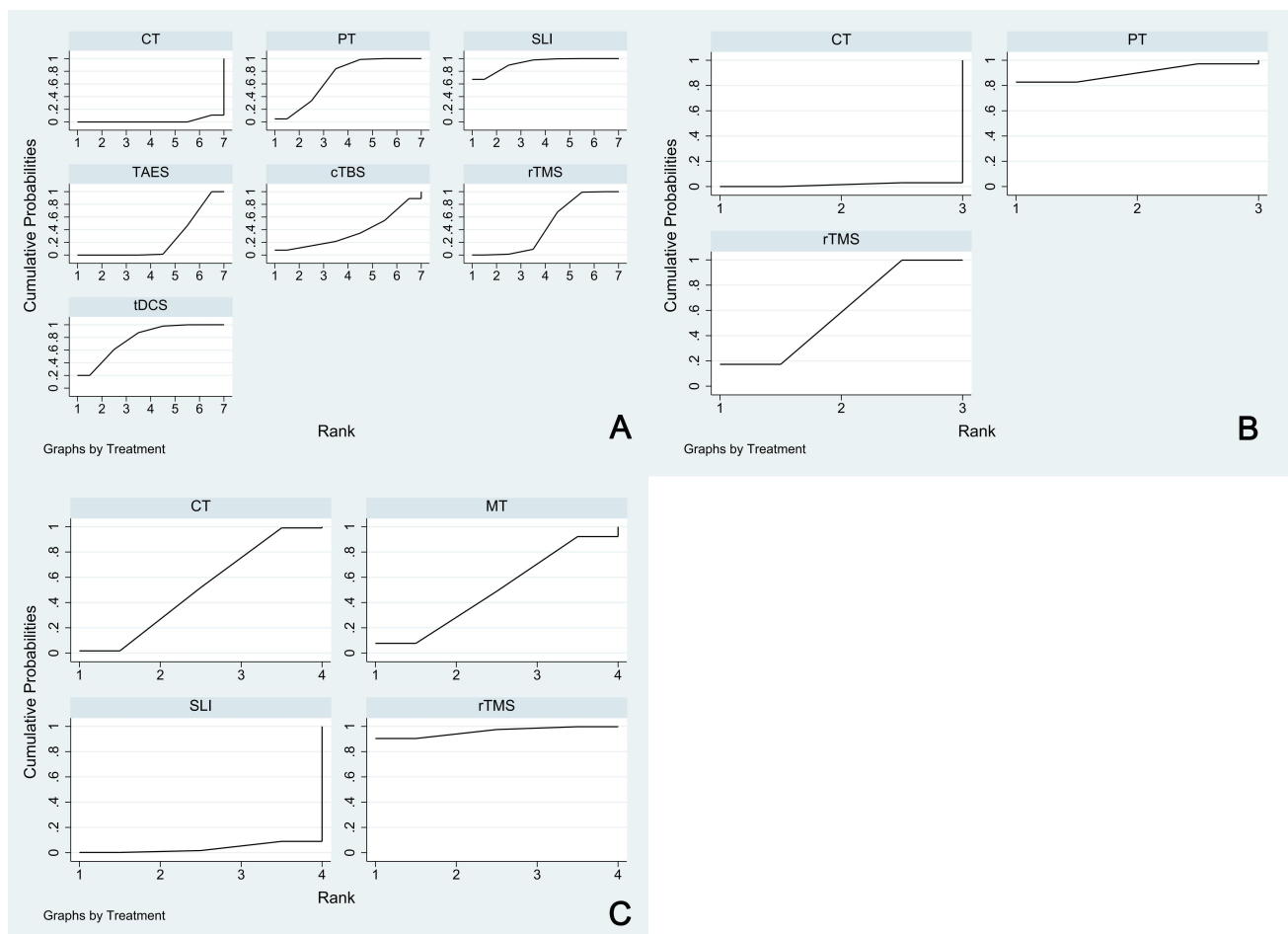
### 3.5 Surface under the Cumulative Ranking Score

#### 3.5.1 Visual Analysis Scale

According to the results of SUCRA, SLI may be the most effective intervention to reduce VAS. The SUCRA probability ranking results were as follows: SLI (92.4%) > tDCS (77.7%) > MT (70.1%) > rTMS (46.3%) > cTBS (37%) > TAES (24.6%) > CT (1.8%). The cumulative probability ranking diagram is shown in Fig. 6A. The area under the curve directly correlates with the effectiveness.

#### 3.5.2 Total Clinical Effective Rate

The results of SUCRA suggest that PT may be the most effective intervention to increase the total clinical ef-



**Fig. 6. Cumulative probability ranking plot.** (A) VAS. (B) Total clinical effective rate. (C) Clinical adverse reaction rate.

fective rate. The SUCRA probability ranking results were as follows: PT (89.9%) > rTMS (58.6%) > CT (1.5%) (Fig. 6B).

### 3.5.3 Clinical Adverse Reaction Rate

According to the results of SUCRA, SLI may be the safest intervention. The SUCRA probability ranking results were as follows: rTMS (95.9%) > MT (49.6%) > CT (50.9%) > SLI (3.6%) (Fig. 6C).

## 4. Discussion

Central Poststroke Pain (CPSP) is one of the most common complications after stroke, and clinical first-line central analgesics often have poor curative effects for patients with strong drug resistance. Invasive neuromodulation therapy is not only expensive but may also be accompanied by serious irreversible sequelae. Therefore, noninvasive complementary therapy has become a research hotspot in the clinical treatment of CPSP. In addition to conventional therapy, this study involved seven noninvasive therapies, which can be roughly divided into ① electric stimulation therapy: rTMS, cTBS, tDCS, and TAES. rTMS and cTBS are two modes of TMS that have a good anal-

gesic effect on neuropathic pain [22]. tDCS is a noninvasive technology that uses a constant, low-intensity direct current (1~2 mA) to regulate the activity of neurons in the cerebral cortex. Studies have also confirmed its effectiveness in the treatment of CPSP [23]. TAES, a new acupuncture treatment method combining transcutaneous electrical nerve stimulation (TENS) with acupuncture and acupoint therapy, has been proven to have analgesic effects and peripheral and central mechanisms similar to acupuncture [24]; ② laser therapy: SLI. As a new technology, SLI is used to alleviate neuropathic pain based on the principle of affecting the stellate ganglion [25]. ③ Psychology therapy: MT and PT. As two branches of psychotherapy, music therapy and mindfulness psychotherapy have gradually begun to receive attention in the clinical treatment of CPSP. The results of this study show ranked the VAS as follows: SLI > tDCS > MT > rTMS > cTBS > TAES > CT; the ranking of total clinical efficacy was PT > rTMS > CT; and clinical adverse reactions ranked as follows: rTMS > MT > CT > SLI.



#### 4.1 Clinical Efficacy

The VAS has obvious advantages in evaluating subjective factors. This method was first used in psychological research [26,27]. Later, VAS scores ranging from 0 to 10 were used to judge the degree of pain [28]. During the evaluation, patients are asked to select the score according to their own feelings. A higher score indicates a more severe degree of subjective pain, and the score value can be accurate. The clinical manifestations of CPSP are diverse, but the main characteristics are pain and sensory disorders. At present, the diagnosis of the disease lacks specificity, and the diagnosis largely depends on the subjective feelings of patients. Therefore, VAS is widely used in the pain assessment of CPSP. The results of this study show that among all non-invasive interventions, SLI is most effective in improving the VAS indicators of patients. The stellate ganglion is the main pathway of the sympathetic nerve. Blocking the stellate ganglion is generally believed to be able to expand the blood vessels in the area dominated by the stellate ganglion. More studies have shown that [29] stellate ganglion block (SGB) therapy can alleviate many drug-resistant headaches and reduce the original dosage of drugs. Invasive stellate ganglion block has achieved a good curative effect, while noninvasive stellate ganglion irradiation, as an alternative therapy for stellate nerve block, is safe and practical [25], but relevant studies on the clinical effect of treating CPSP are scarce. The VAS results of the main indicators in this study suggest that the pain relief effect of SLI is the best, but only one study was included. Therefore, this result is limited to the data analysis of the included literature and cannot completely explain the advantages and disadvantages of each clinical efficacy. Nevertheless, the results rain significance for clinical guidance. The secondary indicator of this study is the total clinical effective rate. The results suggest that PT has the best curative effect. Many CPSP patients often have a certain degree of anxiety and depression when drug efficacy is poor, and anxiety is often accompanied by prostaglandins, bradykinins and other secretions that exacerbate pain, leading to a decrease in the pain threshold. This effect results in emotional fluctuations and a loss of confidence in treatment and prognosis. Therefore, mindfulness psychotherapy, a type of systematic psychotherapy, can have a positive effect on the treatment of central neuralgia and limb rehabilitation of stroke patients by mobilizing the enthusiasm of patients and relieving tension and negative emotions, but sufficient clinical research to further confirm this hypothesis is lacking [30]. However, clinicians often note unexpected effects on CPSP patients with routine drug treatment and psychological treatment in clinical practice.

#### 4.2 Adverse Reactions

Five studies included in this meta-analysis mentioned adverse reactions after the intervention. The intervention measure with the highest adverse reaction rate was rTMS,

which manifested as mild headache, facial twitching or numbness. The adverse reaction rate of SLI was the lowest and mainly manifested as lethargy, dry mouth, and dizziness. All adverse reactions reported in RCTs were mild or transient, and no serious adverse reactions were reported. Therefore, the psychological tension of patients is not excluded. rTMS is a noninvasive neuromodulation therapy based on achieving an analgesic effect with the application of a high-intensity pulsed magnetic field to brain tissue. According to current research, rTMS is effective in the short term and has a limited effect on poststroke central neuralgia. Thus, rTMS is generally considered to not be suitable to be used alone, and other treatment measures, such as combined drug treatment, can improve therapeutic effects [31]. However, attention should be given to evaluation before rTMS treatment in clinical practice to identify patients with intracranial metal implants, cochlear implants, and built-in pulse generators (brain pacemakers, cardiac pacemakers). In this case, rTMS easily causes the built-in pulse generator to fail. Patients with serious physical diseases, those who are using drugs that significantly reduce the threshold of seizures or those who abuse alcohol need to consider the risk-benefit ratio after receiving stimulation treatment, and the use of rTMS is recommended with caution.

#### 4.3 Limitations

In this study, the network meta-analysis method was used for the first time, which can not only compare the indirect and mixed effects between different noninvasive therapies but also compare different treatment schemes for CPSP in the absence of direct comparisons between therapies and identify the best scheme with the greatest probability. This study has the following limitations: (1) Most of the included studies were Chinese studies, and the number of studies was small. Because noninvasive therapy intervention CPSP is a relatively new clinical field, most included studies were drug trials or tested invasive therapies. When studies published in English were included, most of the clinical trials involving noninvasive therapy intervention CPSP were non-RCTs. Except for studies of rTMS, studies on noninvasive therapies are scarce, which may be because rTMS, an alternative therapy of neuromodulation, has long been studied. Consequently, it is more prevalent in the literature. Conversely, other noninvasive therapies are relatively new, and they are not well represented in the literature; (2) The overall quality of the studies was not very high. Although most studies mention random methods, others, such as allocation concealment, blinding methods and potential bias, are not mentioned. (3) The number of RCTs included in the study is insufficient, the sample size is small, with some studies reporting sample sizes of less than 10. Thus, negative results may have not been published. (4) Among the included studies, the length of intervention is somewhat inconsistent, which precludes comparisons between studies and increases clinical heterogeneity; (5) Few outcome

indicators are included in this paper. Others, such as the numerical rating scale (NRS), Hamilton Depression Scale (HAMD), and Hamilton Anxiety Scale (HAMA), are also common outcome indicators of CPSP, but they were not included mainly because too few other outcome indicators were involved in the RCTs included, and this number was insufficient for meta-analysis; (6) Because few studies were included in this work and their quality was poor, most of the studies did not take the patient's family genetic history as the basic research index. However, familial genetic factors play a very important role in the onset and prognosis of stroke. I hope that more studies will include the genetic history as a basic index in the future.

## 5. Conclusions

In summary, noninvasive complementary therapy can effectively alleviate the pain of CPSP patients, and the efficacy and safety of SLI are relatively significant. However, due to the limitations of this study, the efficacy ranking cannot fully explain the advantages and disadvantages of clinical efficacy but only serves as a clinical reference. In the future, we need to continue clinical trials on non-invasive therapy intervention for CPSP and carry out more multicentre, large sample, double-blind clinical randomized controlled trials to supplement and demonstrate the results of this study.

## Availability of Data and Materials

The datasets analyzed in this article are available upon request to: [alis7718@outlook.com](mailto:alis7718@outlook.com).

## Author Contributions

RYL and LNW designed the review. KYC and HYZ collected and analyzed the data. SAX was responsible for the result analysis and make figures. RYL and SAX supervised the procedures. LNW wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.

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## Conflict of Interest

The authors declare no conflict of interest.

## Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.31083/j.jin2204102>.

## References

- [1] Choi-Kwon S, Choi SH, Suh M, Choi S, Cho KH, Nah HW, *et al.* Musculoskeletal and central pain at 1 year post-stroke: associated factors and impact on quality of life. *Acta Neurologica Scandinavica*. 2017; 135: 419–425.
- [2] Nadler M, Pauls M. Shoulder orthoses for the prevention and reduction of hemiplegic shoulder pain and subluxation: systematic review. *Clinical Rehabilitation*. 2017; 31: 444–453.
- [3] Morishita T, Inoue T. Brain Stimulation Therapy for Central Post-Stroke Pain from a Perspective of Interhemispheric Neural Network Remodeling. *Frontiers in Human Neuroscience*. 2016; 10: 166.
- [4] Krames ES, Peckham PH, Rezai AR. *Neuromodulation* (2 volume set) (pp. 6–8). 2nd ed. Academic Press: New York. 2009.
- [5] Hamani C, Fonoff ET, Parravano DC, Silva VA, Galhardoni R, Monaco BA, *et al.* Motor cortex stimulation for chronic neuropathic pain: results of a double-blind randomized study. *Brain: a Journal of Neurology*. 2021; 144: 2994–3004.
- [6] Elias GJB, De Vloo P, Germann J, Boutet A, Gramer RM, Joel SE, *et al.* Mapping the network underpinnings of central post-stroke pain and analgesic neuromodulation. *Pain*. 2020; 161: 2805–2819.
- [7] Chen JS, Liu H, Bai XG, Dong C, Bai L, Zhang AR. To explore the mechanism of TMS in the treatment of post-stroke depression from the perspective of neuroregulation. *Journal of Military Surgeonin in Southwest China*. 2017; 19: 272–274. (In Chinese)
- [8] Sudbrack-Oliveira P, Razza LB, Brunoni AR. Non-invasive cortical stimulation: Transcranial direct current stimulation (tDCS). *International Review of Neurobiology*. 2021; 159: 1–22.
- [9] Matsumura Y, Hirayama T, Yamamoto T. Comparison between pharmacologic evaluation and repetitive transcranial magnetic stimulation-induced analgesia in poststroke pain patients. *Neuromodulation: Journal of the International Neuromodulation Society*. 2013; 16: 349–354.
- [10] Chaimani A, Higgins JPT, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. *PLoS ONE*. 2013; 8: e76654.
- [11] Zhou N, Zhang X. Effect of mindfulness training on thalamic pain after stroke. *China Health Care Nutrition*. 2021; 31: 38, 40. (In Chinese)
- [12] Chen JM, Wang ZY, Wu D, Ni GX. The effect of repeated transcranial magnetic stimulation on sensory threshold in patients with central post stroke pain. *Chinese Journal of Rehabilitation Medicine*. 2020; 35: 820–824+842. (In Chinese)
- [13] Ou HN, Zhou KX, Huang B, Lu WY, Zhu YZ, Qin ZJ, *et al.* Clinical Observation on Transcutaneous Acupoint Electrical Stimulation in the Treatment of Central Nerve Pain with Poststroke Patients. *Chinese Journal of Integrative Medicine on Cardio-/Cerebrovascular Disease*. 2015; 13: 881–883. (In Chinese)
- [14] Guo M, Wang X, Wang WS, Liu X, Zhao L, Bi FL. Effect of music therapy combined with pregabalin on thalamic pain after stroke. *Psychological Monthly*. 2020; 15: 176–177. (In Chinese)
- [15] He BJ, Xia HT, Liang JQ, Zeng DY, Liang YQ, Wang ZQ, *et al.* Evaluation of the effect of super laser irradiation on stellate ganglion combined with pregabalin in the treatment of central neuralgia after stroke. *Journal of China Prescription Drug*. 2022; 20: 110–112. (In Chinese)

- [16] Sun W, Zhao CG, Yuan H, Mou X. Transcranial magnetic stimulation relieves pain and improves cortical excitability after stroke. *Chinese Journal of Physical Medicine and Rehabilitation*. 2019; 252–256.
- [17] Duan Q, Huang XQ, Xiao B, Yuan H, Mou X, Sun W. Effect of continuous theta burst stimulation on motor evoked potentials in patients with central post-stroke pain. *Chinese Journal of Pain Medicine*. 2018; 24: 743–747. (In Chinese)
- [18] Tan J, Li XM, Gou C, Du Y, Wang XM. Study on the analgesic effect of transcranial direct current stimulation on central post-stroke pain. *Journal of North Sichuan Medical College*. 2021; 36: 753–756. (In Chinese)
- [19] Li N, Zhang SM, Tian SP. Effect of repeated transcranial magnetic stimulation combined with carbamazepine on central pain after stroke. *Chinese Journal of Practical Nervous Diseases*. 2016; 19: 52–53. (In Chinese)
- [20] Zhao YY, Wu S, Liu S, Li XW. Analysis of Clinical Efficacy of rTMS in the Treatment of Central Poststroke Pain. *Reflex therapy and Rehabilitation Medicine*. 2021; 2: 134–136. (In Chinese)
- [21] Bae SH, Kim GD, Kim KY. Analgesic effect of transcranial direct current stimulation on central post-stroke pain. *The Tohoku Journal of Experimental Medicine*. 2014; 234: 189–195.
- [22] Zhao CG, Sun W, Ju F, Jiang S, Wang H, Sun XL, *et al*. Analgesic Effects of Navigated Repetitive Transcranial Magnetic Stimulation in Patients With Acute Central Poststroke Pain. *Pain and Therapy*. 2021; 10: 1085–1100.
- [23] Ramger BC, Bader KA, Davies SP, Stewart DA, Ledbetter LS, Simon CB, *et al*. Effects of Non-Invasive Brain Stimulation on Clinical Pain Intensity and Experimental Pain Sensitivity Among Individuals with Central Post-Stroke Pain: A Systematic Review. *Journal of Pain Research*. 2019; 12: 3319–3329.
- [24] Wang ZL, Chen LF, Zhu WM. Observation on the transient analgesic effect of abdominal acupuncture TENS on pain of neck, shoulder, loin and legs. *Zhongguo Zhen Jiu*. 2007; 27: 657–659.
- [25] Wang L, Zhang RJ. Therapeutic effect of super laser irradiation of stellate ganglion on migraine. *Chinese General Practice*. 2015; 18: 1083–1085. (In Chinese)
- [26] Sung YT, Wu JS. The Visual Analogue Scale for Rating, Ranking and Paired-Comparison (VAS-RRP): A new technique for psychological measurement. *Behavior Research Methods*. 2018; 50: 1694–1715.
- [27] Paul-Dauphin A, Guillemin F, Virion JM, Briançon S. Bias and precision in visual analogue scales: a randomized controlled trial. *American Journal of Epidemiology*. 1999; 150: 1117–1127.
- [28] Ko KJ, Cho WJ, Lee YS, Choi J, Byun HJ, Lee KS. Comparison of the Efficacy Between Transurethral Coagulation and Transurethral Resection of Hunner Lesion in Interstitial Cystitis/Bladder Pain Syndrome Patients: A Prospective Randomized Controlled Trial. *European Urology*. 2020; 77: 644–651.
- [29] Kortüm FC, Bräscher AK, Schmitz-Buchholz D, Feldmann RE, Jr, Benrath J. Interventional pain therapy. Results of a survey among specialized pain physicians in Germany. *Schmerz (Berlin, Germany)*. 2014; 28: 591–599. (In German)
- [30] Lu M. Research progress in the diagnosis and treatment of central pain after stroke. *Chinese Journal of Cerebrovascular Diseases*. 2016; 13: 325–328. (In Chinese)
- [31] Flaster M, Meresh E, Rao M, Biller J. Central poststroke pain: current diagnosis and treatment. *Topics in Stroke Rehabilitation*. 2013; 20: 116–123.