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REVIEW

Optimal Method of Electrical Stimulation for the Treatment of Upper Limb Dysfunction After Stroke: A Systematic Review and Bayesian Network Meta-Analysis of Randomized Controlled Trials

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Background: The obstacle of limb motor caused by stroke, especially the decline of motor function of upper limbs, can directly affect the activities of daily living of stroke patients with hemiplegia. Based on long-term clinical practice, the treatment effect of electrical stimulation methods for stroke limb dysfunction has been widely recognized and supported by authoritative guidelines and systematic reviews. However, which electrical stimulation method is the optimum in the treatment of stroke limb dysfunction is still a controversial issue.

Objective: In this paper, we adopted Network Meta-Analysis (NMA) to rank the priorities of various electrical stimulation methods, so as to select the optimal electrical stimulation method and discuss its rationality in guiding clinical practice.

Methods: We carried out a systematic review by searching a total of 6806 studies from 8 databases and 2 clinical trial registries, and finally screened out 34 studies for further investigation. Then, pairwise meta-analysis and Bayesian network meta-analysis were employed to evaluate the effectiveness and ranking of various interventions. The primary outcome measure was Fugl-Meyer Assessment Upper Extremity (FMA-UE), and the secondary outcome measures were Modified Barthel Index (MBI) and Modified Ashworth Scale (MAS). Finally, the risk of bias, publication bias and sensitivity of the Randomized Controlled Trials (RCTs) were evaluated.

Results: On the basis of comprehensive rehabilitation treatment (RT), the Functional Electrical Stimulation (FES) was superior than other electrical stimulation methods in improving both FMA-UE and MBI. Meanwhile, the results indicated that the Transcutaneous Electrical Acupoint Stimulation (TEAS) was the only electrical stimulation method that showed treatment advantages in reducing MAS.

Conclusion: The study showed that FES had the optimal overall rehabilitation effect on upper limb dysfunction of stroke patients based on the comprehensive RT, while the treatment effect of TEAS on upper limb spasticity after stroke was the most significant.

Keywords: network meta-analysis, electrical stimulation, stroke, upper limb dysfunction

Background

Stroke is a kind of cerebral blood circulation disorder which can cause motor dysfunction, and it has become one of the main causes of disability in the elderly.[1] A global epidemiological prediction report on nervous system diseases shows that stroke has been accounted for a larger proportion of the global disease burden in recent years.[2] The motor dysfunction of limbs caused by stroke,

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especially the decline of motor function of disabled upper limbs, can directly have an adverse effect on activities of daily living of stroke patients with hemiplegia. A number of studies show that 30–66% of the patients with hemiplegia after stroke still have no motor function in their upper limbs 6 months later.[3] Various of treatment methods have been applied to the treatment of this kind of disease, but it is still very tricky to select an optimal treatment method when determining the treatment scheme for the recovery of upper limb function.[4] The rehabilitation of upper limb dysfunction after stroke is still one of the difficulties in the treatment of stroke-related sequelae.

At present, in the Rehabilitation Treatment (RT) of stroke patients with hemiplegia, various rehabilitation techniques based on the concepts and theories of Bobath, Rood, Brunnstrom and Proprioceptive Neuromuscular Facilitation (PNF) are the primary rehabilitation training methods. Recently, an increasing number of novel treatments have been applied to the rehabilitation of stroke patients with upper limb motor dysfunction, including Virtual Reality (VR),[5] Brain-machine Interface (BI),[6] Mental Practice (MP),[7] extracorporeal shock wave therapy,[8] music therapy[9,10] and so on. However, the effect of these novel treatments in clinical practice has not been fully verified. It is still a burning issue for clinicians to use practical and effective treatments based on traditional rehabilitation. The electrical stimulation has been widely regarded as an effective approach for the treatment of stroke limb dysfunction through long-term clinical practice.[11]

Diverse electrical stimulation methods have been applied in medical field. The frequently adopted methods for limb dysfunction after stroke are including: Transcutaneous Electrical Nerve Stimulation (TENS), Neuromuscular Electrical Stimulation (NMES), Functional Electrical Stimulation (FES), Transcranial Direct Current Stimulation (tDCS) and Transcutaneous Electrical Acupoint Stimulation (TEAS). TENS is transdermal output pulse current to effectively control the pain and stimulate the sensory, thus increasing muscle power and movement function and decreasing spasticity.[12] TEAS is basically the combination of TENS and acupuncture points. FES is the electrical stimulation of motor neurons to stimulate muscle contraction and generate/increase joint torque. Some researchers define FES as electrical stimulation applied in voluntary movement.[13] NMES typically adopts higher frequencies (20–50 Hz) and can be used to produce muscle tetany and contraction for "functional" purposes.[14] tDCS works by applying a weak and constant direct current to the brain and is capable of enhancing or suppressing cortical excitability.[15] During the past few years, many efforts have been dedicated to the systematic reviews and meta-analyses on the effect of the above electrical stimulation methods in the treatment of upper limb dysfunction after stroke. Vafadar et al[16] studied the effect of FES on preventing or reducing shoulder subluxation in early stage after stroke. Eraifej et al[13] investigated the effect of FES on improving activities of daily living and motor function after stroke. Elsner et al[17] proposed that tDCS can improve the activities of daily living and cognitive function of stroke patients. Nevertheless, it can be found that most of the research concentrates on only one type of electrical stimulation method or isolated upper limb parts (such as hand, elbow, shoulder). There is a lack of comprehensive analysis and discussion on the treatment effect of various electrical stimulation methods in the related public literature. Generally, more than one rehabilitation treatments are adopted as the basic treatment method in the actual clinical treatment process.[18,19] Therefore, it is extremely essential to study and select an optimal electrical stimulation method for upper limb motor dysfunction after stroke based on comprehensive RT. In this paper, we applied NMA to establish a network of RCTs by combining direct and indirect evidence in the network of RCTs to compare different treatment schemes. NMA, also known as multiple treatment meta-analysis or mixed treatment comparison, is an extension of paired meta-analysis, allowing more than two interventions to be compared in a single and coherent analysis of all relevant RCTs.[20] Since NMA can contribute to evaluate the comparative effectiveness of different treatment methods frequently used in clinical practice, it has triggered a widespread attention among clinicians.[21] Systematic assessment of RCTs has been generally considered to be the authoritative evidence to verify the effectiveness of interventions.[22,23] Based on the proposed approach, we employed NMA to rank the priority of different electrical stimulation methods aiming at selecting an optimal electrical stimulation method and discussing its rationality in guiding clinical practice.

Methods

This study abided by the PRISMA-NMA guide.[24] (Additional file 1) And a version of this study was registered on Open Science Framework (Registration DOI: 10.17605/OSF.IO/TAZ8D).

Search Strategy

In order to ensure the sufficient number of selected literature, the retrieval time was set from the establishment date of each database to July 20, 2021. The literature language was set within Chinese and English. The search databases included: China National Knowledge Infrastructure (CNKI), VIP Database for Chinese Technical Periodicals (VIP), WANFANG Database (WF), Chinese biomedical literature service system (SinoMed), PubMed, Web of Science (WOS), Embase, and Cochrane Library. The clinical trial registries included the International Standard Randomized Controlled Trial Number (ISRCTN) Register and the Chinese Clinical Trial Registry (ChiCTR). In addition, MeSH terms and free words used in this study included: (1) transcutaneous electrical nerve stimulation, transcutaneous electrical acupoint stimulation, neuromuscular electrical stimulation, functional electrical stimulation et al (2) stroke, cerebrovascular accident, brain vascular accident et al (3) randomized controlled trials, clinical trials et al. Taking PubMed database as an example, the complete data retrieval strategy is shown in Table 1.

Table 1 Data Retrieval Strategy for PubMed Database

Steps	Search
#1	"Electric Stimulation[MeSH]" OR "Electric Stimulation Therapy[Ti/Ab]" OR "Electrotherapy[Ti/Ab]" OR "transcutaneous electrical nerve stimulation[MeSH]" OR "Transcutaneous Electric Stimulation[Ti/Ab]" OR "Percutaneous Electric Nerve Stimulation[Ti/Ab]" OR "TENS[Ti/Ab]" OR "Transcutaneous Electrical Stimulation [Ti/Ab]" OR "Transdermal Electrostimulation[Ti/Ab]" OR "transcutaneous electrical acupoint stimulation[Ti/Ab]" OR "TEAS[Ti/Ab]" OR "neuromuscular electrical stimulation [Ti/Ab]" OR "NMES[Ti/Ab]" OR "functional electrical stimulation[Ti/Ab]" OR "FES[Ti/Ab]" OR "Transcranial Direct Current Stimulation[Ti/Ab]" OR "tDCS[Ti/Ab]"
#2	"Stroke[MeSH]" OR "Cerebrovascular Accident[Ti/Ab]" OR "CVA[Ti/Ab]' OR 'Brain Vascular Accident[Ti/Ab]' OR 'Apoplexy[Ti/Ab]"
#3	"randomized controlled trial[PT]" OR "controlled clinical trial[PT]" OR "randomized[Ti/Ab]" OR "clinical trials as topic[MeSH]" OR "randomly[Ti/Ab]" OR "trial[Ti]" OR "clinical[Ti]"
#4	"Hemiplegia[MeSH]" OR "Paralysis[MeSH]" OR "Upper limb[Ti/Ab]" OR "Upper extremity[Ti/Ab]" OR "shoulder [Ti/Ab]" OR "arm[Ti/Ab]" OR "forearm[Ti/Ab]" OR "wrist [Ti/Ab]" OR "hand[Ti/Ab]" OR "finger[Ti/Ab]" OR "motor function[Ti/Ab]"
#5	#1 AND #2 AND #3 AND #4

Inclusion and Exclusion Criteria

Type of Study

All the included literature covered the journal articles of both Chinese and English RCTs based on all selected databases from the establishment date of the database to July 20, 2021. There was no restriction on the publication status of articles in this paper. The excluded types were conference articles, newspaper articles, and book abstracts in all databases. Meanwhile, master's and doctoral theses were included as well. Moreover, negative results may be achieved in the case of that the included patients are far from enough. In this case, the intervention was actually effective. However, due to the small sample size, false negative results were produced.[25] Therefore, for the purpose of ensuring the quality of the included literature and reducing the bias of this study, we excluded the literature with a total sample size of less than 30.

Type of Participant

The patients in the included literature were supposed to meet the relevant diagnostic criteria of ischemic or hemorrhagic stroke. This study had no restrictions on gender, age, course of disease and race of patients. The excluded types were hemiplegia or limb dysfunction caused by various other reasons, such as Spinal Cord Injury (SCI).

Type of Intervention

All the included literature was required to meet implementation standards of intervention set by us for both experimental and control group. The specified standards were as follows: (1) The experimental group should include one or more methods of TENS, FES, NMES, TEAS, tDCS combined with RT. Due to the complexity of the condition of stroke patients, the RT techniques used in RCTs are not be exactly same. We consulted the relevant guidelines[26,27] in the preliminary work. The scope of RT was determined on the basis of the guidelines and combined with clinical practice. RT should cover various comprehensive RT methods, such as exercise therapy, occupational therapy, rehabilitation training, rehabilitation education, functional exercise, conventional drug treatment as well as routine nursing for stroke. (2) The control group should include one or more methods of TENS, FES, NMES, TEAS, tDCS combined with RT (same as the experimental group) or only RT; in the meantime, RT combined with Sham Stimulation (SS) should be also included in this group.

The excluded interventions were following: (1) The research focus of the experimental group or the control group was a certain rehabilitation therapy, such as stretching training and mirror therapy combined with electrical stimulation, rather than comprehensive rehabilitation therapy. (2) The comparisons of different stimulation sites, stimulation frequency, stimulation methods and stimulation duration between the same or different kinds of electrical stimulation. Furthermore, if the intervention methods for the different groups in multi-arm studies were identical, but the intervention measures were different, we would combine the data of the two groups. In addition, there were no restrictions on the treatment dose, stimulation site, treatment duration and treatment frequency of electrical stimulation.

Type of Outcome Measure

In the present paper, the primary outcome measure was FMA-UE, and the secondary outcome measures were MBI and MAS. FMA-UE is a well-designed, feasible and effective clinical examination method, which has been widely used in motor function evaluation of stroke patients.[28] MAS is a frequently-used clinical assessment tool for muscle tone increase, which is mainly used to assess spasticity caused by stroke.[29] MBI was adopted to evaluate the activities of daily living, thus reflecting the improvement of limb dysfunction.[30] It is worth mentioning that the baseline data is the first evaluation data before the first treatment, and the outcome measure data is the first evaluation data after the last treatment. In addition, studies that did not use any of the specified outcomes were excluded.

Study Screening Process

Firstly, we adopted the aforementioned search strategy to retrieve relevant studies from databases (CNKI, VIP, WF, SinoMed, PubMed, WOS, Embase and Cochrane Library) and the clinical trial registries (ISRCTN and ChiCTR), and then imported them into NoteExpress (V3.4.0) database. Subsequently, two professionally trained reviewers (LW and YT) would conduct a preliminary screening for all studies. Only the studies with complete titles and abstracts meeting the above inclusion criteria can be preliminarily screened out for further study. Besides, the studies with incomplete titles and abstracts were marked and would be re-screened in the following steps. Finally, the reviewers would review the preliminary selected studies thoroughly, and further screened out the studies completely meeting the inclusion criteria. In order to ensure the objectivity and reliability of the selected results, the two reviewers were required to select independently. If there were divergences between the two reviewers, the third professional reviewer (YF) would intervene in for further evaluation.

Data Processing and Analysis Process

The data extraction of the included studies was carried out by two professional reviewers (YX and SH) independently. The extracted data included title, reviewer's name, publication time, country, stroke type and classification, course of disease, sample size and sample proportion, age, sex ratio, intervention method, treatment cycle and outcome measure (mean and standard deviation).

We used Review Manager (Revman V5.3) and Aggregate Data Drug Information System (ADDIS V1.16.8) to implement the meta-analysis. Pairwise meta-analysis was adopted for direct comparison. Where there was no significant heterogeneity ($I^2 < 50\%$), we used the fixed effect model for comprehensive analysis. Whereas if there was obvious heterogeneity between studies ($I^2 \geq 50\%$), the random effect model would be adopted. A Markov chain Monte Carlo method was used to conduct NMA using the ADDIS. The NMA network plots of three outcome measures were generated in Stata software (V16.0 MP). For any possible situation, NMA was performed only when different interventions were connected into a network. Moreover, the node-splitting method was employed to divide the evidence of each comparison into direct evidence and indirect evidence. The surface under the cumulative ranking curve (SUCRA) was used to rank the advantages and disadvantages of different electrical stimulation methods.

Risk of Bias Assessment

In this study, the Cochrane Collaboration risk of bias tool was used to assess the bias risk of RCTs. The assessment items included: (1) Random sequence generation (selection bias); (2) Allocation concealment (selection bias); (3) Blinding of participants and personnel (performance bias); (4) Blinding of outcome assessment (detection bias); (5) Incomplete outcome data (attrition bias); (6) Selective reporting (reporting bias); (7) Other bias. The assessment results would be divided into high risk (H), low risk (L) and unclear risk (N). If all of the assessment items of one trial were low risk, or there were less than three unclear risk items, the trial would be finally judged as low risk. If two or more assessment items of one trial were high risk,

the trial would be considered as high risk.[31] Other trials would be classified as unclear risk.

Publication Bias Assessment

The publication bias was assessed by funnel plots generated by Stata software.

Sensitivity Analysis

We evaluated the robustness of each result by sensitivity analyses, excluding high-risk bias studies.

Results

Literature Research

In this study, a total of 6806 studies were retrieved from eight databases and two clinical trial registries. A total of 342 studies meeting the basic inclusion criteria were preliminarily selected after the titles and abstracts reviewed by two reviewers. Then, the preliminary selected studies would be thoroughly reviewed by the other two reviewers. Meanwhile, the third reviewer would be involved to re-evaluate the studies selected for further study. Finally, a total of 34 RCTs[32–65] were included in this study. The specific study screening process is illustrated in Figure 1.

In this study, a total of 34 RCTs with 2383 patients, of which 46 patients dropped out during the trial were included. The details of all included studies are shown in Additional file 2. As the progress of stroke has a dramatic impact on the upper limb motor function, most studies described the baseline data of stroke types and course (duration of stroke). Only 7 studies[32,33,35,36,48,52,54] accurately described the stroke stages, and 13 studies[32,34,38,39,41,43–47,49,55,61] specified Brunnstrom stages. The types of stroke were classified as ischemic or hemorrhagic in all studies describing stroke types, whereas the course of stroke were not specified in four studies describing the stroke course.[33,36,53,57] Except that the patient allocation ratio of the two studies[59,63] was 1:1:1, the allocation ratio of the other studies was 1:1. One study[33] only described the average age, while another study[53] described the overall age and sex ratio of patients without distinguishing between the control group and the experimental group. Other trials had detailed age and sex baseline data. Additionally, the interventions, treatment cycles and outcome measures of all studies were complete.

Since there were no restrictions on the treatment dose, stimulation site, treatment duration and treatment frequency of electrical stimulation in inclusion criteria, in order to ensure the continuity and integrity of this study, the two reviewers independently sorted out the information of the above influencing factors during the study data entry stage. The details are shown in Additional file 3. In most studies, the frequency/intensity, site and duration of the same electrical stimulation were roughly the same, while the frequency/intensity of different electrical stimulation were quite different, which was related to the basic stimulation dose required by different electrical stimulation treatments. The treatment frequency was mainly once a day, and 5 days a week.

The results of bias risk assessment are illustrated in Figures 2 and 3, and the detailed assessment results are shown in Additional file 4. The results indicated that 5 trials were not classified into high-risk category by standard random allocation method, 4 trials of which[56,58,61,64] were allocated according to the order of inclusion, and one of which[37] was grouped according to the wishes of patients and their families. 5 trials[44,51,55,62,63] were classified as high risk due to the inappropriate adopted blinding method. Moreover, 8 trials[33,34,43,47,56,59,63,65] had other high-risk biases, including 4 trials in which the gender ratio of patients in the two groups was seriously unbalanced, 4 trials in which the proportion of stroke types was significantly different between the two groups, and one trial in which the course of disease was considerably different between the two groups. Among the 8 trials, one trial[59] with a drop-out rate >20% at 8 weeks of follow-up was also included due to the complete outcome measure data after 4 weeks of treatment. In addition, it can be found that there was no high-risk bias trial related to 4 assessment items, including allocation concealment (selection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), blinding of outcome assessment (detection bias). In general, two trials[56,63] were classified as high-risk overall bias, accounting for 5.9%.

Pairwise Meta-Analysis

In the present paper, the two intervention methods were compared comprehensively by pairwise meta-analysis. The results are shown in Additional file 5. The results of three outcome measures are summarized in Table 2, highlighting the intervention groups with meaningful comprehensive effects. When we used FMA-UE to evaluate the trial results, the treatment effect of FES, tDCS, TENS or TEAS combined with RT was superior than that of RT. When we adopted MBI to evaluate the trial results, the FES, tDCS or TEAS combined with RT outperformed RT. As for MAS, the treatment effect of TEAS combined with RT was better than that of RT. Meanwhile, compared with RT, the tDCS combined with RT had a more desirable

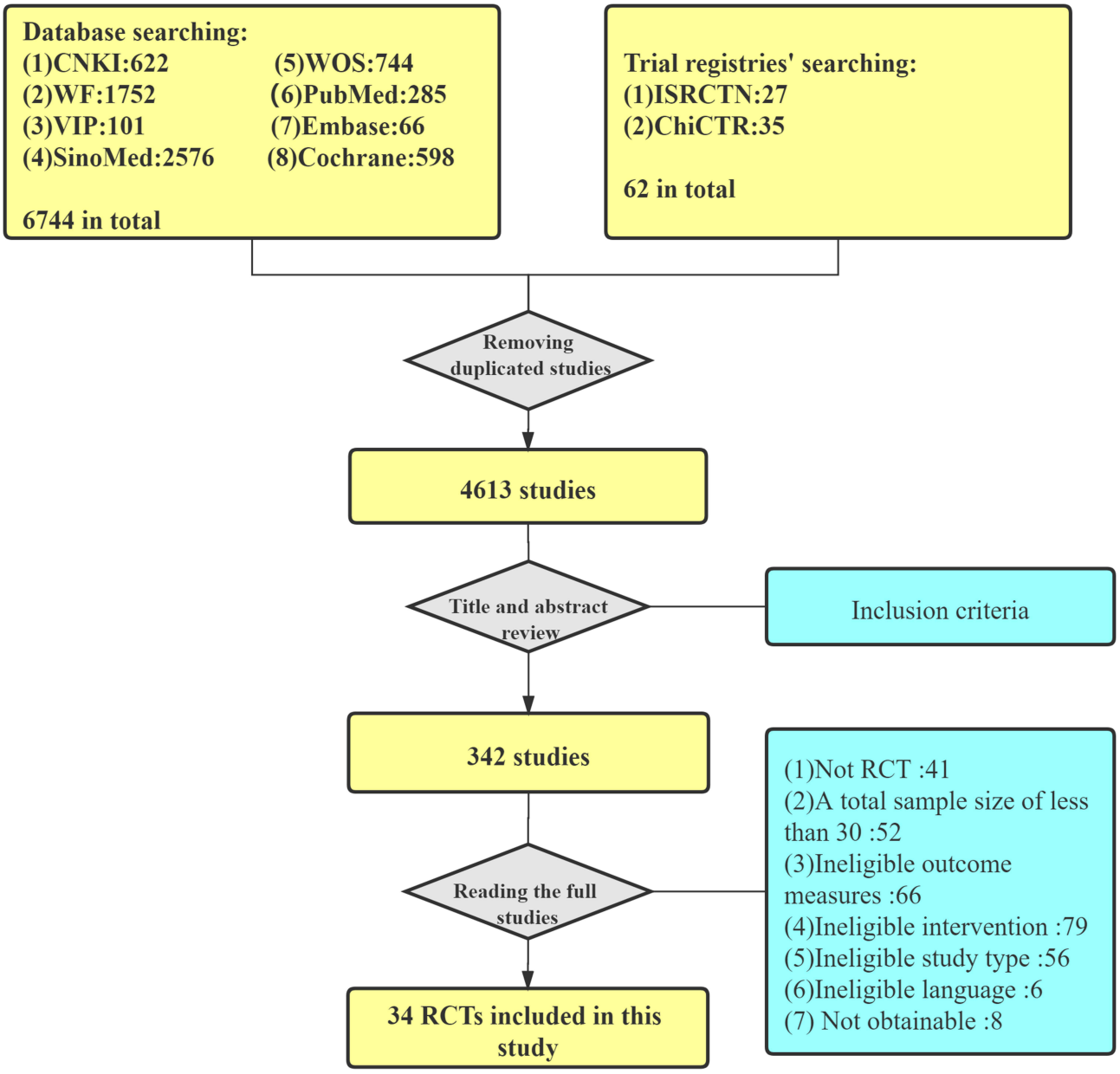

Figure 1 Flow chart of study selection.

treatment effect using FMA-UE and MBI to evaluate. In addition, in a trial adopting MAS for evaluation,[38] the treatment effect of tDCS combined with RT surpassed that of RT combined with SS.

Network Meta-Analysis

Figures 4–6 depict the network plots of different interventions for three outcome measures. The node size of each intervention represents the total number of patients included in the RCTs, and the thickness of the line between two nodes represents the total number of RCTs involving the two groups of interventions. FMA-UE and MBI were used for the evaluation of 7 interventions respectively, and MAS was used to evaluate 6 interventions. To be specific, FMA-UE was the outcome measure for 33 trials involving 1927 patient in total; MBI was the outcome measure for 27 trials with a total of 1648 patients; MAS was the outcome measure for 12 trials with 624 patients. As shown in Figures 4 and 5, the network structures among the interventions evaluated by FMA-UE and MBI were approximately the same. The primary difference is the number of patients with different interventions and RCTs, indicating that FMA-UE and MBI were common outcome measures for evaluating the

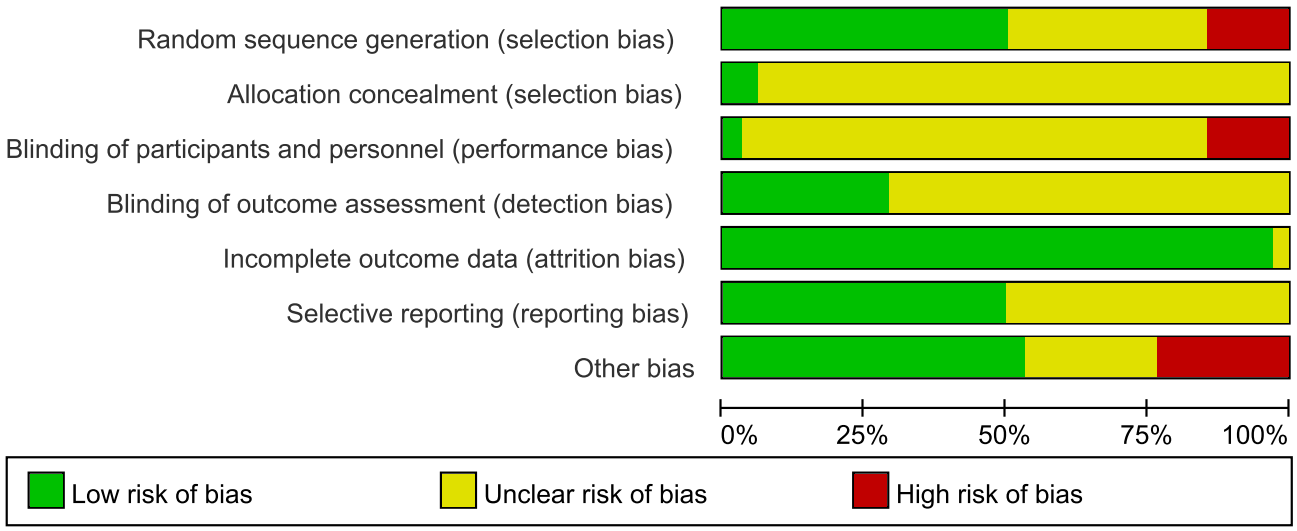

Figure 2 Risk of bias graph.

rehabilitation of upper limb dysfunction after stroke. As illustrated in Figure 6, the trials without using FES were evaluated by MAS, and the number of trials and patients involved is less than that involved in FMA-UE and MBI. It is worth noting that the trials of tDCS combined with RT and SS combined with RT were not directly related to other intervention groups, and the number of trials and patients was also small. In general, except for RT, TEAS or NMES combined with RT had the largest number of trials and patients.

Since the interventions of one group of trials (RT+tDCS vs RT+SS) from the MAS network plot were independent of any interventions of other trials (shown in Figure 6), and this group of trials did not meet the requirements for subsequent NMA, it cannot be processed by Stata software. Thus, this group of trials was excluded for further analysis.

The effectiveness of NMA results depended on the internal consistency of the evidence network: the sources of direct evidence and various indirect evidence should be consistent.[66] In this study, we adopted the segmented node method to test inconsistency in the NMA (Additional file 6). The results indicated that the direct or indirect comparisons of each segmented node had no statistical significance ($p>0.05$), demonstrating that there was no evidence of design inconsistency. We tested the convergence of the model, and the potential scale reduction factor was 1 (Additional file 7).

Figures 7 and 8 show the NMA results. It can be seen from the figures that in terms of improving FMA-UE score, FES, TEAS and TENS combined with RT were better than RT. In the meantime, the treatment effect of FES combined with RT was superior than that of NMES, TENS and SS combined with RT. In addition, the treatment effect of SS combined with RT was inferior than that of TEAS, TENS and tDCS combined with RT. When it comes to improving MBI score, FES, TEAS and tDCS combined with RT outperformed RT. On the basis of RT, the treatment effect of TEAS, tDCS and FES were better than that of SS, and the treatment effect of NMES was not as desirable as that of TEAS. The decrease of MAS score represents the relief of upper limb spasm. The treatment effect of TEAS combined with RT was more excellent than that of RT. Moreover, there was no significant treatment effect among the other interventions.

In this paper, we adopted a consistent model using ADDIS to rank various interventions in NMA, and the results were illustrated as ranking probability matrix (Figures 9–11). The ranking value corresponding to each intervention represented its probability. It can be seen from Figure 9 that FES combined RT was the most effective method to promote the FMA-UE score, followed by TEAS, tDCS, TENS and NMES. TEAS had the most significant effect on improving the MBI score (Figure 10). Additionally, TEAS had an optimal effect on reducing the MAS score (Figure 11). The SUCRA scores are specified in Additional file 8.

Sensitivity Analysis

Sensitivity analysis was carried out for all pairwise meta-analyses after excluding trials with high-risk bias. The results indicated that the treatment effect of NMES

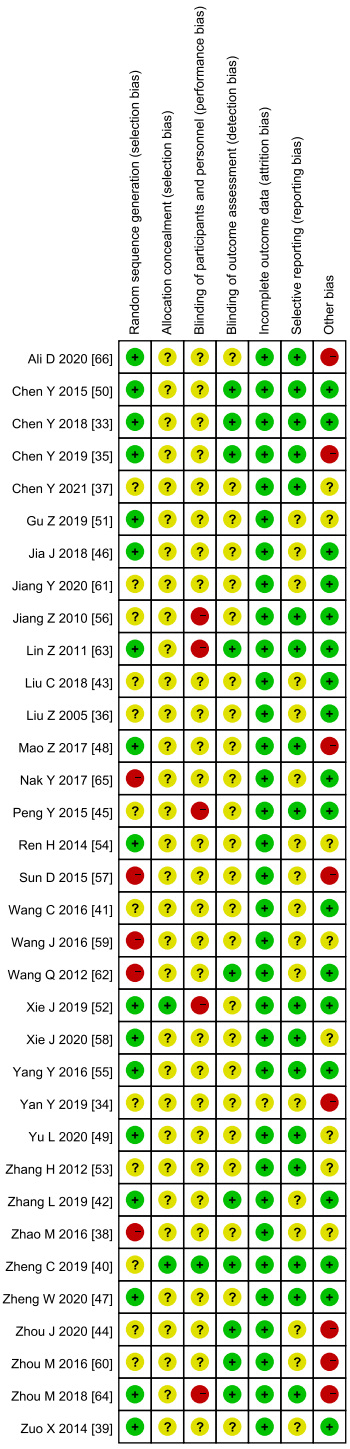

Figure 3 Risk of bias summary.

combined with RT was superior than that of RT (SMD 0.71, 95% CI (0.06, 1.73)).

Publication Bias

The funnel plots were used to evaluate the publication bias (Figures 12–14). As shown in these figures, the quantity distributions of trials involved in the three outcome measures were relatively symmetrical. Due to the limited sample size of RCTs, most trials were distributed in the lower middle part of the figures. As for all of the three outcome measures, there were a small number of trials outside the 95% confidence interval, indicating that there was potential heterogeneity in these trials. Furthermore, the missing angle of MBI (Figure 13) on the left side of the red vertical line (odds ratio=0) may be relevant to the unpublished trials with negative results.

Adverse Events

In the present paper, a total of 4 RCTs had adverse events with 12 patients having adverse reactions. Among these RCTs, two trials[38,39] using tDCS combined with RT had 7 patients with skin discomfort, of which 2 patients had sleep disorders at the same time, of which 1 patient had dizziness under SS treatment. In one trial,[51] one patient in the experimental group had severe shoulder pain under NMES combined with RT, and the other patient in the control group had recurrent cerebral infarction only under RT. In another trial,[63] 2 patients with poor physical conditions used non-steroidal anti-inflammatory drugs during the follow-up period, and had aggravated shoulder pain caused by improper care.

Discussion

Main Findings

We conducted a systematic review and Bayesian network meta-analysis on the relevant evidence of 34 RCTs (including 2383 patients). Various common electrical stimulation methods for the treatment of limb dysfunction after stroke were selected for the study in this paper, including FES, NMES, TEAS, TENS and tDCS. Among them, TEAS is within the scope of TENS. At present, TEAS has been widely used in the treatment of various diseases, and multiple relevant RCTs have been carried out.[67] Therefore, we studied TEAS independently of TENS in this paper. Although the above 5 electrical stimulation methods have been extensively adopted in clinic, the strengths and weaknesses of these methods still need to be further investigated.

It can be deduced from the results that all of the selected electrical stimulation methods are effective in improving FMA-UE and MBI scores. Nevertheless, compared with other studies, some studies[61–63] presented an opposite trend in MAS, which may be related to the course

Table 2 The Results of Three Outcome Measures

Outcome Measure	Comparison	Number	SMD (95% CI)	I^2(%)	P
FMA-UE	**RT+FES vs RT**	4	**2.57(1.16, 3.98)**	95%	<0.00001
	RT+NMES vs RT	5	0.58(−0.02, 1.18)	76%	0.002
	RT+tDCS vs RT	1	**0.72(0.30,1.14)**	-	-
	RT+tDCS vs RT+SS	5	**0.61(0.36,0.86)**	24%	0.26
	RT+TEAS vs RT	10	**1.16(0.61,1.70)**	90%	<0.00001
	RT+TEAS vs RT+SS	2	1.72(−0.76,4.19)	95%	<0.00001
	RT+TENS vs RT	4	**0.71(0.12,1.30)**	74%	0.01
	RT+TENS vs RT+NMES	2	0.07(−0.47,0.61)	0%	0.92
MBI	**RT+FES vs RT**	3	**1.09(0.26,1.91)**	79%	0.009
	RT+NMES vs RT	5	0.44(−0.04,0.91)	63%	0.03
	RT+tDCS vs RT	1	**0.97(0.54,1.40)**	-	-
	RT+tDCS vs RT+SS	3	**0.56(0.27,0.85)**	0%	0.4
	RT+TEAS vs RT	9	**0.92(0.45,1.38)**	89%	<0.00001
	RT+TEAS vs RT+SS	2	1.24(−0.44,2.91)	91%	0.0008
	RT+TENS vs RT	2	0.21(−0.38,0.81)	0%	0.97
	RT+TENS vs RT+NMES	2	0.19(−0.35,0.73)	0%	1
MAS	RT+NMES vs RT	3	0.12(−0.47,0.70)	56%	0.1
	RT+tDCS vs RT+SS	1	**0.70(0.06,1.34)**	-	-
	RT+TEAS vs RT	6	**0.93(0.36,1.50)**	83%	<0.0001
	RT+TENS vs RT	1	−0.12(−0.94,0.69)	-	-
	RT+TENS vs RT+NMES	1	−0.11(−0.80,0.58)	-	-

Note: The bold values indicates a statistical difference.

Abbreviations: RT, Rehabilitation Treatment; FES, Functional Electrical Stimulation; TENS, Transcutaneous Electrical Nerve Stimulation; TEAS, Transcutaneous Electrical Acupoint Stimulation; NMES, Neuromuscular Electrical Stimulation; tDCS, Transcranial Direct Current Stimulation; SS, Sham Stimulation; FMA-UE, Fugl-Meyer Assessment for Upper Extremity; MBI, Modified Barthel Index; MAS, Modified Ashworth Scale.

of the disease of the patient. Besides, unlike the points system of FMA-UE and MBI, MAS adopts the rating system to evaluate the condition of patients,[68] implying that the variation trend of MAS may better reflect the change rule of the disease. In pairwise meta analysis and NMA, whether FMA-UE or MBI was used for evaluation, FES presented an optimal treatment effect. Some scholars have done relevant research and found the advantages of FES in the treatment of upper limb dysfunction after stroke.[13] Recent studies[69,70] have indicated that this may be related to the fact that FES can induce more plasticity changes and brain remodeling. Nevertheless, taking the uncontrollable factors of interventions into account, the RCTs included in this study did not consider some FES that were not widely used in clinic or need additional devices, such as brain computer interface, EMG biofeedback or new auxiliary electrical stimulation devices. We intended to systematically study on various new treatment schemes of FES in the future.

It has been proved that TEAS and tDCS were also effective treatment methods. Especially when reducing the MAS, TEAS was the only electrical stimulation method that showed treatment advantages, demonstrating that it had a significant effect on improving upper limb spasm after stroke. In the meantime, TENS did not show the same effect as TEAS, indicating that the combination of traditional Chinese medicine acupuncture points can improve the effect of electrical stimulation to a certain extent. Moreover, it should also be noted that only one trial of TENS evaluated by MAS was included, and this trial was classified as a high-risk bias due to the large difference between the experimental group and the control group, so the results may be biased. More high-quality RCTs need to be conducted in the future to further verify this result. Furthermore, NMES was not as effective as the other 4 electrical stimulation methods. It can be seen from the ranking probability matrix (Figures 9 and 10) that NMES ranked fifth in improving the scores of FMA-UE and MBI. As shown in the network plots (Figures 4–6), the number of RCTs involving NMES was second only to that involving TEAS, and so did the number of patients. In clinic, NMES has been extensively adopted for patients with limb function after stroke, but its treatment effect remains to be further investigated. Some studies have shown that NMES has limitations in recovering motor function, which may be related to the recruitment of

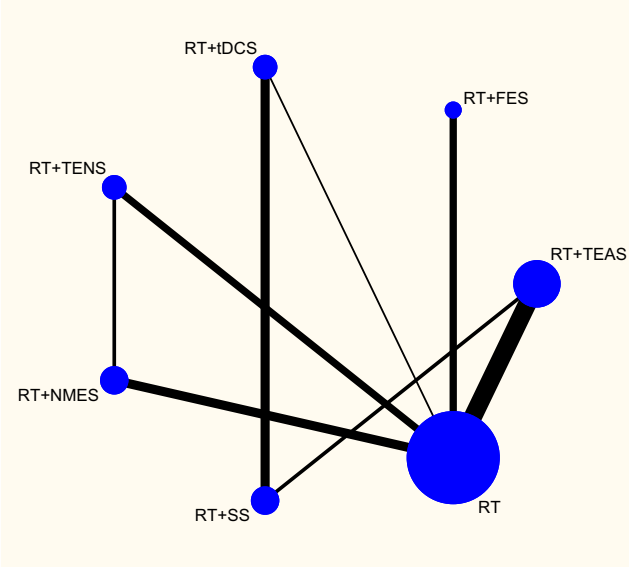

Figure 4 Network plot of FMA-UE.
Abbreviations: RT, Rehabilitation Treatment; FES, Functional Electrical Stimulation; TENS, Transcutaneous Electrical Nerve Stimulation; TEAS, Transcutaneous Electrical Acupoint stimulation; NMES, Neuromuscular Electrical Stimulation; tDCS, Transcranial Direct Current Stimulation; SS, Sham Stimulation.

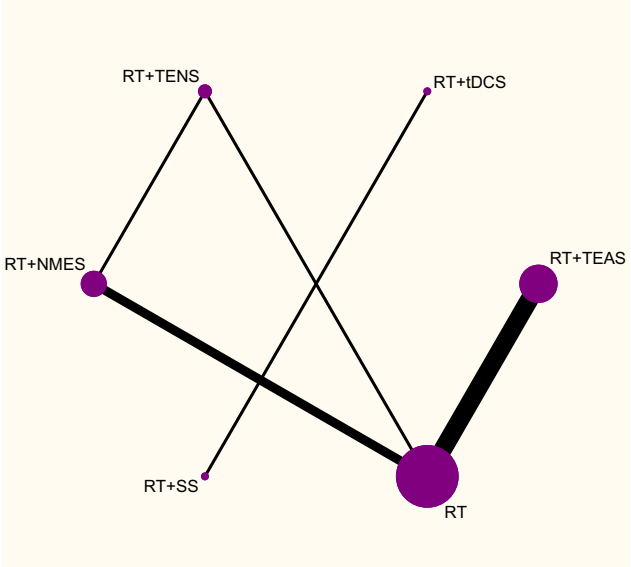

Figure 6 Network plot of MAS.
Abbreviations: RT, Rehabilitation Treatment; TENS, Transcutaneous Electrical Nerve Stimulation; TEAS, Transcutaneous Electrical Acupoint Stimulation; NMES, Neuromuscular Electrical Stimulation; tDCS, Transcranial Direct Current Stimulation; SS, Sham Stimulation.

motor units.[71,72] Some researchers have claimed that the actual clinical treatment effect of NMES depends on the systematic treatment scheme.[73]

In addition, the treatment effect of either RT or SS was the worst. However, it is interesting to find out that the treatment effect of RT alone was better than that of RT combined with SS in the evaluation of FMA-UE and MAS. On the one hand, it may prove that the placebo effect of SS on patients is not strong enough. On the other hand, it may also be related to the publication bias.

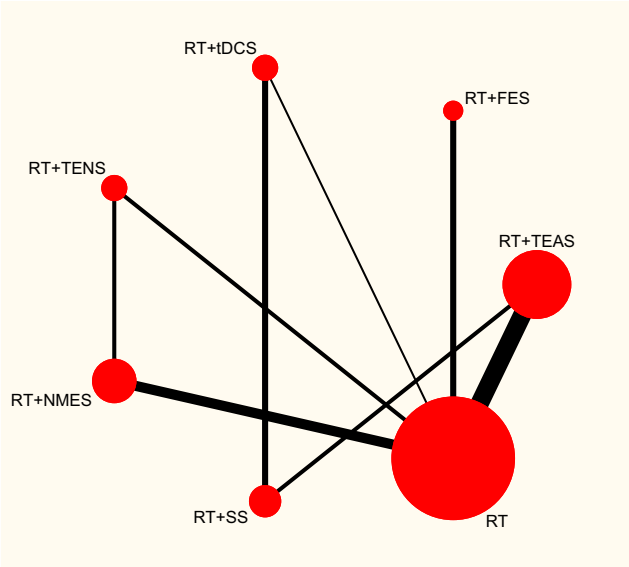

Figure 5 Network plot of MBI.
Abbreviations: RT, Rehabilitation Treatment; FES, Functional Electrical Stimulation; TENS, Transcutaneous Electrical Nerve Stimulation; TEAS, Transcutaneous Electrical Acupoint Stimulation; NMES, Neuromuscular Electrical Stimulation; tDCS, Transcranial Direct Current Stimulation; SS, Sham Stimulation.

Overall Quality of Evidence

In this study, the RCTs included in the study have been carefully selected. The results manifested that four RCTs had adverse events. To be specific, a total of 12 patients had adverse reactions, most of the adverse reactions were local skin discomfort, and only one patient had recurrent cerebral infarction during RT. Consequently, it was proved that the electrical stimulation methods were safe.

Unlike the drug test, it is quite hard to realize double blindness in the actual clinical practice. The blinding of participants or personnel is impractical for various electrical stimulation methods. For instance, it is difficult for personnel to be unaware of whether the electrical stimulator is on during the trials. After evaluating each trial through the Cochrane Collaboration risk of bias tool, we found that only three trials[44,55,63] clearly did not use the blind method, one trial[39] clearly used blind method, and other trials did not clarified the relevant information. Unblinded results may bias the final comprehensive effect evaluation. On average, unblinded evaluators of subjective binary outcomes generated substantially biased effect estimates in randomized clinical trials, exaggerating the odds

Treatment	MBI						
FMA-UE	RT	**9.28 (3.48, 14.66)**	4.80 (-0.37, 9.59)	-1.15 (-8.36, 5.76)	**10.71 (7.36, 13.80)**	7.42 (-2.00, 16.95)	**8.56 (1.35, 15.66)**
	-12.28 (-16.22, -8.26)	RT+FES	-4.50 (-11.98, 2.97)	**-10.41 (-19.52, -1.14)**	1.45 (-5.05, 7.87)	-1.82 (-12.72, 9.16)	-0.64 (-9.79, 8.49)
	-4.20 (-8.57, 0.04)	**8.05 (2.17, 13.93)**	RT+NMES	-5.98 (-14.30, 2.95)	**5.94 (0.17, 11.74)**	2.72 (-6.22, 11.87)	3.74 (-4.55, 12.56)
	2.82 (-3.69, 9.29)	**15.11 (7.53, 22.84)**	7.08 (-0.77, 14.79)	RT+SS	**11.93 (5.04, 18.57)**	8.56 (-3.06, 20.55)	**9.77 (4.17, 15.32)**
	-8.65 (-11.43, -5.83)	3.61 (-1.31, 8.50)	-4.46 (-9.62, 0.70)	**-11.50 (-17.63, -5.02)**	RT+TEAS	-3.37 (-13.00, 6.95)	-2.22 (-9.24, 5.06)
	-5.63 (-10.40, -0.78)	**6.63 (0.44, 12.97)**	-1.42 (-7.20, 4.38)	**-8.46 (-16.56, -0.17)**	3.03 (-2.42, 8.67)	RT+TENS	1.13 (-11.00, 12.79)
	-5.50 (-12.13, 1.42)	6.82 (-0.85, 14.73)	-1.32 (-9.17, 6.73)	**-8.30 (-12.60, -4.02)**	3.17 (-3.49, 9.77)	0.17 (-8.13, 8.36)	RT+tDCS

Figure 7 Network meta-analysis results for FMA-UE and MBI.
Notes: The bold values indicates a statistical difference.
Abbreviations: RT, Rehabilitation Treatment; FES, Functional Electrical Stimulation; TENS, Transcutaneous Electrical Nerve Stimulation; TEAS, Transcutaneous Electrical Acupoint Stimulation; NMES, Neuromuscular Electrical Stimulation; tDCS, Transcranial Direct Current Stimulation; SS, Sham Stimulation; FMA-UE, Fugl-Meyer Assessment for Upper Extremity; MBI, Modified Barthel Index.

ratio by 36%.[74] As a result, the evaluation of the results of such trials should be treated carefully.

Based on the above reasons, we conducted the sensitivity analyses, and the results showed that most of the results were reliable. Moreover, publication bias also deserved attention. As for all of the three outcome measures, there were a small number of trials outside the 95% confidence interval, indicating that there was potential heterogeneity in these trials. Additionally, the missing angle of MBI (Figure 13) on the left side of the red vertical line (odds ratio=0) may be relevant to the unpublished trials with negative results.[75,76] Furthermore, when it was not clear whether some trial data were normally distributed, we did not convert the quartile and the median or the minimum/maximum of the median into the mean and standard deviation, thus influencing the publication bias to a some degree. In this study, the research team carried out a comprehensive search of 8 databases and 2 clinical trial registries, and even searched for unpublished data. The asymmetric funnel plot (Figure 14) indicated that

Treatment	-			
MAS	RT	-	-	-
	-0.08 (-0.55, 0.39)	RT+NMES	-	-
	-0.46 (-0.76, -0.16)	-0.38 (-0.93, 0.19)	RT+TEAS	-
	0.16 (-0.88, 1.22)	0.24 (-0.78, 1.26)	0.62 (-0.46, 1.70)	RT+TENS

Figure 8 Network meta-analysis results for MAS.
Note: The bold values indicates a statistical difference.
Abbreviations: RT, Rehabilitation Treatment; TENS, Transcutaneous Electrical Nerve Stimulation; TEAS, Transcutaneous Electrical Acupoint Stimulation; NMES, Neuromuscular Electrical Stimulation; MAS, Modified Ashworth Scale.

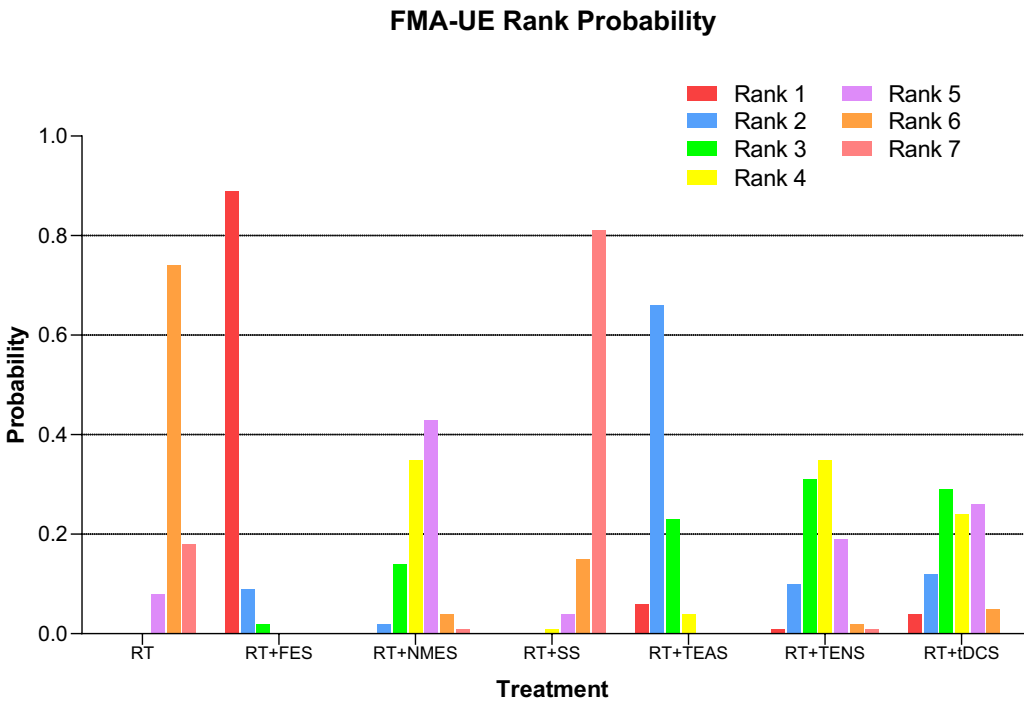

Figure 9 Ranking probability figure for reduction in FMA-UE.
Note: Rank 1 is best, rank N is worst.
Abbreviations: RT, Rehabilitation Treatment; FES, Functional Electrical Stimulation; TENS, Transcutaneous Electrical Nerve Stimulation; TEAS, Transcutaneous Electrical Acupoint Stimulation; NMES, Neuromuscular Electrical Stimulation; tDCS, Transcranial Direct Current Stimulation; SS, Sham Stimulation; FMA-UE, Fugl-Meyer Assessment for Upper Extremity.

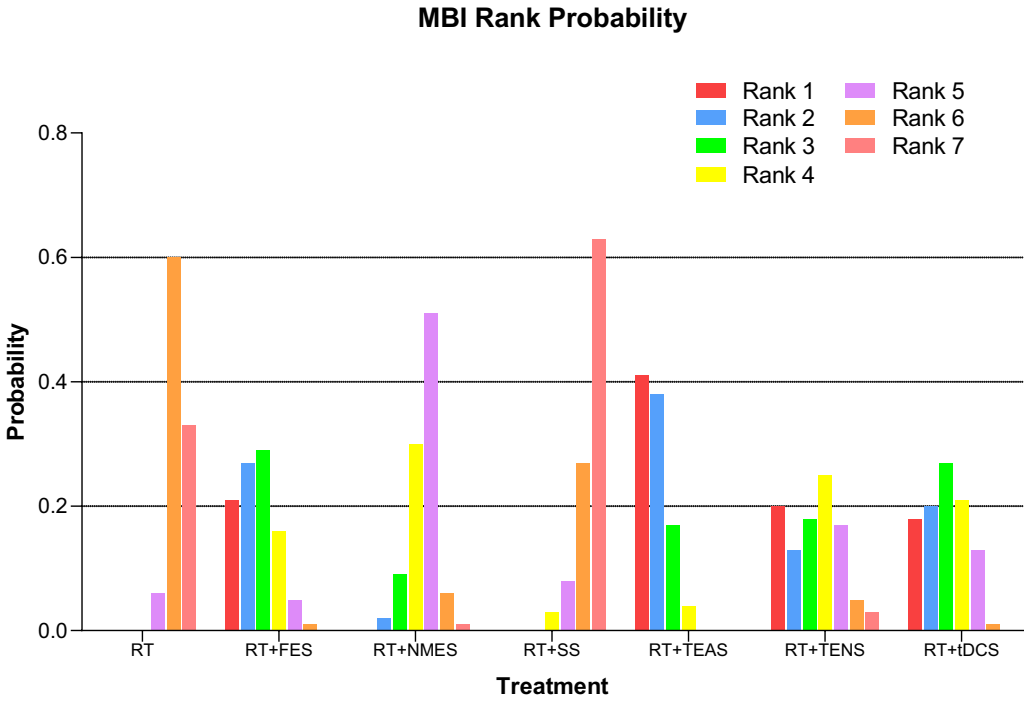

Figure 10 Ranking probability figure for reduction in MBI.
Note: Rank 1 is best, rank N is worst.
Abbreviations: RT, Rehabilitation Treatment; FES, Functional Electrical Stimulation; TENS, Transcutaneous Electrical Nerve Stimulation; TEAS, Transcutaneous Electrical Acupoint Stimulation; NMES, Neuromuscular Electrical Stimulation; tDCS, Transcranial Direct Current Stimulation; SS, Sham Stimulation; MBI, Modified Barthel Index.

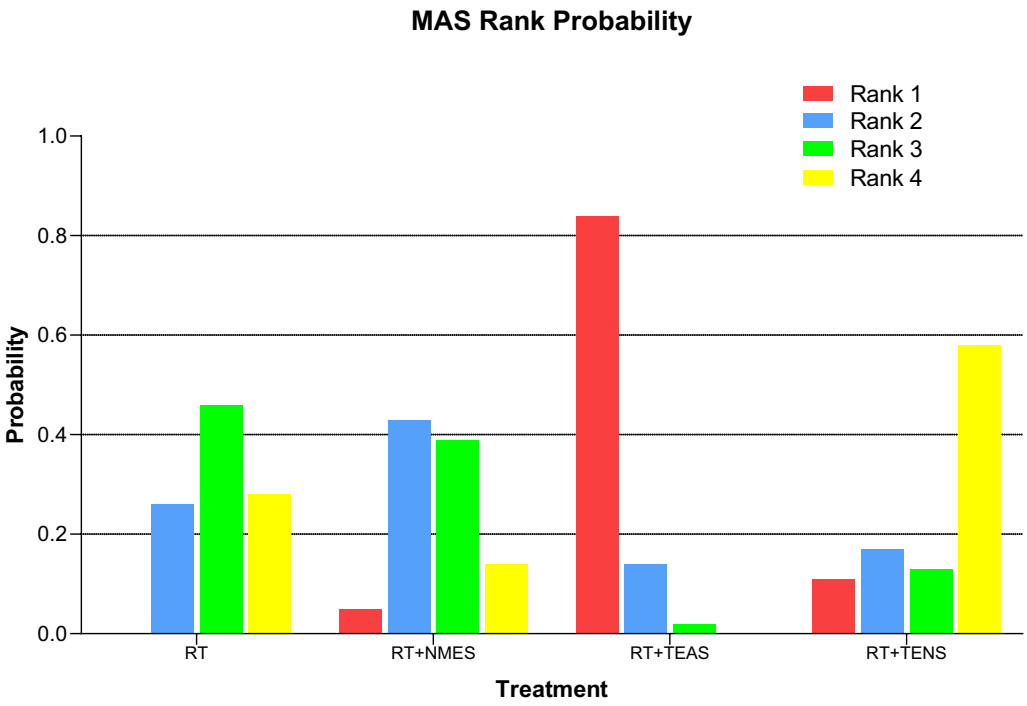

Figure 11 Ranking probability figure for reduction in MAS.
Note: Rank 1 is best, rank N is worst.
Abbreviations: RT, Rehabilitation Treatment; TENS, Transcutaneous Electrical Nerve Stimulation; TEAS, Transcutaneous Electrical Acupoint Stimulation; NMES, Neuromuscular Electrical Stimulation; MAS, Modified Ashworth Scale.

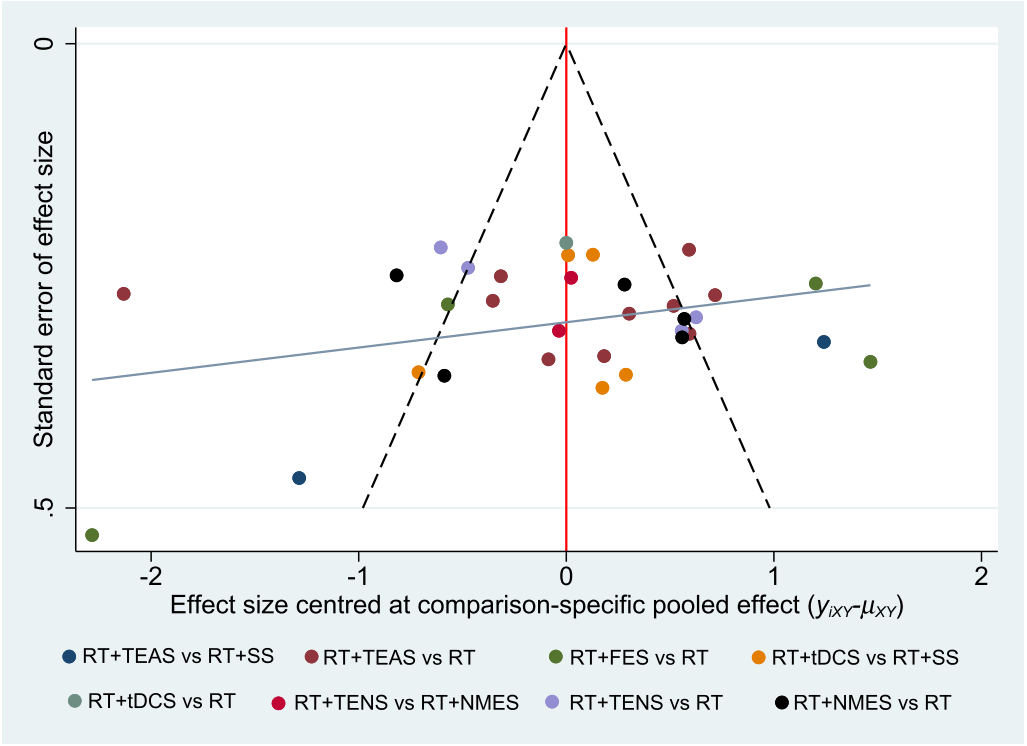

Figure 12 Funnel plot for the network meta-analysis of reduction in FMA-UE.
Abbreviations: RT, Rehabilitation Treatment; FES, Functional Electrical Stimulation; TENS, Transcutaneous Electrical Nerve Stimulation; TEAS, Transcutaneous Electrical Acupoint Stimulation; NMES, Neuromuscular Electrical Stimulation; tDCS, Transcranial Direct Current Stimulation; SS, Sham Stimulation.

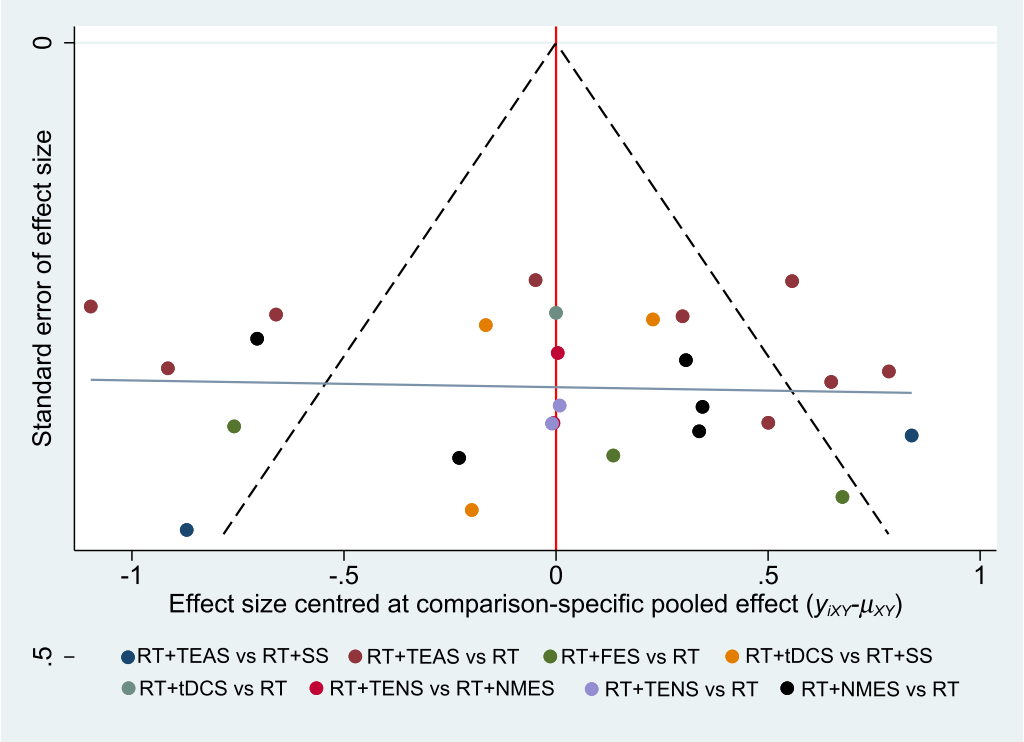

Figure 13 Funnel plot for the network meta-analysis of reduction in MBI.
Abbreviations: RT, Rehabilitation Treatment; FES, Functional Electrical Stimulation; TENS, Transcutaneous Electrical Nerve Stimulation; TEAS, Transcutaneous Electrical Acupoint Stimulation; NMES, Neuromuscular Electrical Stimulation; tDCS, Transcranial Direct Current Stimulation; SS, Sham Stimulation.

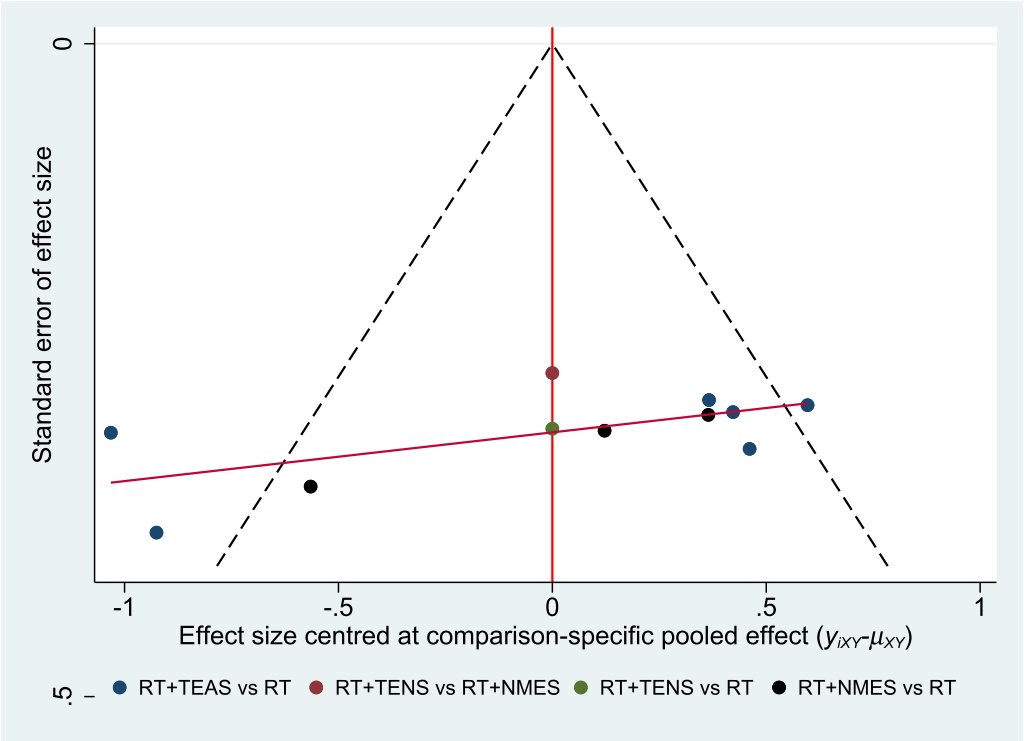

Figure 14 Funnel plot for the network meta-analysis of reduction in MAS.
Abbreviations: RT, Rehabilitation Treatment; TENS, Transcutaneous Electrical Nerve Stimulation; TEAS, Transcutaneous Electrical Acupoint Stimulation; NMES, Neuromuscular Electrical Stimulation.

there may be small-study effects in the whole network.[77] However, considering the comprehensive retrieval in the early stage of this study, we did not regard the asymmetry of the funnel plot as a specific evidence of publication bias.[78]

Strengths and Limitations

The strengths of this study are as follows. Firstly, this study was conducted according to PRISMA-NMA[24] and PRISMA guidelines and checklist.[79] In order to ensure the reliability of the final conclusion, the research team implemented a comprehensive search of 8 databases and 2 clinical trial registries, including RCTs only. Secondly, the Bayesian analysis approach adopted in this study was more accurate than the frequency-based methods. In addition, there were few relevant studies on the treatment effect comparison of different electrical stimulation methods for upper limb dysfunction after stroke, and this was the first academic study to investigate five different electrical stimulation methods and comprehensively compare their treatment effects on the basis of comprehensive RT. Furthermore, we made efforts to get the included trials closer to clinical practice by strictly restricting comprehensive RT methods, thus making the results have more guiding significance for clinicians.

Nevertheless, this study still has some limitations. First of all, most RCTs did not accurately describe the stages of stroke, and the duration of some trials varied significantly, which had a dramatic impact on the baseline data and outcome measure data. Besides, the dose settings (including frequency and current) of various electrical stimulation methods or the same electrical stimulation in different RCTs were quite different, and there was no standard for dose setting. Moreover, the specific stimulation site, treatment duration and treatment frequency of the same electrical stimulation method in different RCTs were also various. In this paper, we did not set any restrictions on the above influencing factors, but this may increase the risk of research bias. In the future, we will study the frequency/intensity of the same or different electrical stimulation methods in detail. Second, the language limitations of the literature, the differences of patient gender and acupoint selection of TEAS may lead to heterogeneity. Third, the two studies[60,63] were three-arm tests. We divided them into three groups for comparison of different interventions, but each group had small sample size, which may reduce the reliability of the analysis results. Finally, the statistical results show that there were 50% of the studies received project funding, which may also affect the heterogeneity of the study. However, limited by the amount of research data, we did not take the impact of this factor into account.

Conclusions

This study provides plenty of effective and convincing evidence for electrical stimulation in the treatment of upper limb dysfunction after stroke. The results indicate that on the basis of comprehensive rehabilitation treatment, FES is superior than other electrical stimulation methods in improving the scores (FMA-UE and MBI) of stroke patients with upper limb dysfunction. Meanwhile, it is proved that TEAS is the only electrical stimulation method showing treatment strengths in reducing the MAS rating, indicating that TEAS has a significant effect on improving upper limb spasm after stroke. However, due to the limitations of the number of studies included and various details of RCTs, more high-quality RCTs are required to provide strong evidence to support the results.

Abbreviations

NMA, Network Meta-Analysis; FMA-UE, Fugl-Meyer Assessment for Upper Extremity; MBI, Modified Barthel Index; MAS, Modified Ashworth Scale; FES, Functional Electrical Stimulation; TENS, Transcutaneous Electrical Nerve Stimulation; TEAS, Transcutaneous Electrical Acupoint Stimulation; NMES, Neuromuscular Electrical Stimulation; tDCS, Transcranial Direct Current Stimulation; RT, Rehabilitation Treatment; PNF, Proprioceptive Neuromuscular Facilitation; VR, Virtual Reality; BI, Brain-machine Interface; MP, Mental Practice; RCT, Randomized Controlled Trial; CNKI, China National Knowledge Infrastructure; VIP, VIP Database for Chinese Technical Periodical; WF, WANFANG Database; SinoMed, Chinese biomedical literature service system; WOS, Web of Science; ISRCTN, International Standard Randomised Controlled Trial Number Register; ChiCTR, Chinese Clinical Trial Registry; Revman, Review Manager software; SMD, Standardized Mean Difference; SUCRA, Surface Under The Cumulative Ranking Curve; SCI, Spinal Cord Injury; SS, Sham Stimulation.

Data Sharing Statement

All data relevant to the study are included in the article or uploaded as supplementary information.

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Author Contributions

YT designed the study and write the manuscript. LW implemented the thought with software, analyzed the data. YX and SH screened the literature and extracted the relevant data and evaluated the quality of RCTs. YT and JH dedicated in results analysis and manuscript revision. YF participated into analysis implementation and organized discussion of the results. All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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