Meta-analysis of clinical trials of transcranial magnetic stimulation for chronic pelvic pain syndrome

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Abstract

Background: In recent years, repeated transcranial magnetic stimulation (rTMS) has been used in clinical trials for the treatment of chronic pelvic pain syndrome, but its efficacy needs to be further verified.

Objectives/Methods: This meta-analysis aimed to evaluate the efficacy and safety of transcranial magnetic stimulation in the treatment of chronic pelvic pain syndrome. Databases of PubMed, the Cochrane Library, Embase, CNKI, VIP, Wanfang, and SinoMed were searched for all clinical trials published before Nov.08.2021. The effect size was evaluated by using the standardized mean difference (SMD) and a 95% confidence interval (CI).

Results: We included 7 studies comprising 99 participants. VAS scale was used as the main index of pain intensity, was observed (SMD=0.19, 95%CI -0.07 to 0.42, p=0.13) has no treatment effect. Reduction in depression ,anxiety and symptoms were not find out, there was a significant effect of quality of life (SF-36, SMD= -8.69, 95%CI -12.04 to -5.35, p 0.00001). No serious adverse events were reported by the included articles.

Conclusion: TMS may improve ADL, and long-term interventions of rTMS have a positive impact on pain and mood in patients with CPPS. However, these findings should be interpreted with caution due to the limitations of the included studies.

Introduction

Chronic pelvic pain (CPP) is a group of diseases or syndromes that last for more than 6 months and are caused by various functional or/and organic causes with pain in the pelvis and its surrounding tissues as the main symptom[1, 2]. Chronic pelvic pain syndrome (CPPS) is a series of symptoms caused by complex causes such as endometriosis, irritable bowel syndrome, interstitial cystitis, and pudendal neuralgia, which are disturbed in 15% – 25% of women each year[3, 4]. They will not only be interfered with by long-term severe pain interference by gastrointestinal problems, emotional changes, and even seriously affect the normal life and work. The complex long-term treatment of CPP makes many sick women refuse to visit the hospital, and it has been shown that CPPS causes a considerable economic burden on women and the health care system internationally[5].

The treatment of CPPS is usually based on the UPOINT system classification and requires multidisciplinary professional treatment[6]. Patients with CPPS account for 12% of hysterectomies and 40% of laparoscopies each year, and only 10–15% of patients meet the surgical criteria. However, many patients not only do not recover for a long time but also have a series of complications after surgical treatment. Postoperative complications such as postoperative adhesion, organic pain, and infection make rehabilitation more difficult [7–9]. Patients who continue to suffer from pain symptoms after medical and surgical treatment often choose to try manual, aerobic exercise, and cognitive therapy for intervention[10, 11].

Nowadays, physical therapy has produced significant results as a more comfortable treatment option. Among them, transcranial magnetic stimulation, as a noninvasive brain stimulation technique, is widely used in the treatment of complex neuropathic pain. The pathomechanism of CPPS may be due to abnormal central nervous sensitization, an imbalance of the excitatory and inhibitory systems[12]. Repetitive transcranial magnetic stimulation (rTMS) may be considered a safe method to regulate cortical excitability and pain thresholds, and the analgesic effect of rTMS can be confirmed in some patients who are resistant to medical treatment, mentioned in a Meta-analysis on rTMS for chronic neurological pain[13, 14].

In a case report using rTMS to stimulate M1 for refractory pelvic and perineal pain, Louppe et al proposed the idea of treatment with neuroregulation technology for the first time[15]. For some CPPS patients, they were still affected by pain after drug surgical treatment and various peripheral treatment. At this time, two weeks after rTMS treatment, the pain was significantly relieved. Since then, continuous studies have proved the influence of rTMS on neuropathic pain in complex regions [16–19]. Recent systematic reviews have shown that rTMS has a positive effect on the treatment of chronic pain, mainly in patients' pain, psychological disorders, gastrointestinal digestive disorders, and urogenital system disorders [14]. The use of rTMS in the treatment of chronic pain is relatively well studied and the efficacy and safety of treatment options are well established. There is currently no review of the efficacy of rTMS in treating CPPS. According to previous literature [20–23], there are differences in treatment outcomes, a variety of treatment regimens, and the choice of outcome assessment indicators is not constant. Therefore, it is necessary to summarize and discuss these studies to provide clinical reference evidence for future use of rTMS in treating CPPS.

Methods

Protocol and registration

Our meta-analysis followed the PRISMA statement and confirmed that all methods followed in accordance with PRISMA guidelines and regulations (Supplementary material: PRISMA-2020-checklist). The protocol of this study was registered at the International Prospective Register of Systematic Review, PROSPERO, under the identification CRD42021284974 and can be integrally assessed online(https://www.crd.york.ac.uk/prospero/#recordDetails).

Search strategy

The database of PubMed, the Cochrane Library, Embase, CNKI, VIP, Wanfang, and SinoMed were searched for all clinical trials published before Nov.08.2021. The search terms were “Transcranial magnetic stimulation, chronic pelvic pain syndrome”. The search was limited to human studies. Manual searches of the reference lists of the pertinent articles were also conducted to identify relevant articles.

Study Selection

Initial screening was based on titles and abstracts. As the CPPS covers a wide range of types, all of the articles that we were in the initial screening were retained that met the disease types in the EAU Guidelines. Two reviewers independently assessed these articles for eligibility. In case of disagreement, the two

reviewers checked the full text of the article and discussed with each other to reach an agreement. The articles were then all assessed. Studies were included if they met the following criteria: (1) belonged to a clinical trial, regardless of the type of trial; (2) did not include chronic myofascial syndrome not specified as trigger point; (3) patients were adults (≥ 18 years); (4) results included at least pain scores; and (5) the type of intervention was rTMS.

Quality Appraisal Assessment

Each included study was individually assessed by two reviewers, Two reviewers (WMY and CHY) independently evaluated risk of bias of included studies using Cochrane Collaboration's tool for assessing the risk of bias. The six recommended domains involving seven items included selective bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessors), attrition bias (incomplete outcome data), reporting bias (selective reporting) and other bias. The overall judgment for each study was classified as "low", "high" or "unclear" based on the degree of bias. Discrepancies between reviewers were resolved by the third reviewer (RX).

Data Extraction

Literature search, study identification and data extraction were conducted between November 2021 and December 2021. All searched records were imported into the reference management software (EndNote x9) to eliminate duplicate records. The full texts of the studies that potentially met the inclusion criteria were obtained to further evaluate their eligibility. Any disagreements were resolved by discussion with the third reviewer (RX). Data were extracted by one reviewer (WMY) using the prepared form and checked for accuracy by another reviewer (CHY).

The standard form was jointly designed by two reviewers to collect relevant data from each study to obtain the following information: (1) patient characteristics; (2) trial design; (3) rTMS treatment protocol; (4) outcome measures; and (5) the duration of follow-up.

Data Synthesis and Analysis

Review Manager software V.5.3 provided by Cochrane Collaboration was used for the statistical analysis, and the statistical significance was defined as two-sided p value of < 0.05. Data were summarised using relative risk with 95% CI for binary outcomes, as well as mean difference (MD) or normalized MD (SMD) and corresponding 95% CI for continuous outcomes. However, when the heterogeneity among studies was high (I^2 > 75%), the overall pooled analysis was considered inappropriate, and it was considered that the statistical heterogeneity among the included studies was very serious according to the causes of heterogeneity, including different assessment tools, differences in subjects, design of trial protocols. If the results were presented only graphically, the Get Data Graphic Digitizer 2.26 was used (Fig. https://getdata.com/) The software extracts the required data.

Results

Study Identification

Of the total 217 studies found after the initial database search, 7 were identified (N = 99). The flow chart of the selection process is shown in Fig. 1. Four studies came from France, the rest were the United Kingdom, Finland, Italy. The number of participants ranged from 30 to 76 years, and the duration of illness ranged from 1.4 to 28.5 years, of which 66.6% were female. Transcranial magnetic stimulation was applied in all included studies [15, 20–25]. Three studies were IBS patients [20, 23, 24], two pudendal neuralgia [15, 21], one endometriosis[22], and one CP/CPPS [25], Except for one case report [15], all other studies were part of the parallel sham control and crossover sham control trials. Patients with chronic myofascial syndrome in an unspecified area of disease were excluded from the included studies. Only one study [20] used rTMS as a single treatment; the cross over sham control trial results only took data before uncrossing. One of the study [24] patients received 1 hour of stimulation, and the remaining studies were treated for an average of 4.83 weeks. All studies were published in English. The details of the included studies and the results of quality assessment are shown in Tables 1 respectively.

The targeted brain area was M1 in 6 interventions and DLPFC in 1 interventions; all studies were Hf-rTMS at frequencies ≥ 10 Hz, the total number of pulses was 1500 in three studies, the total number of pulses was 2000 in three studies. There were two articles with stimulation intensity of 110% rMT and five articles with 80% rMT. The figure-of-eight coil was used in four studies, one was an H-coil [20], the remaining two were not reported, and five studies were followed up.

Table 1
Characteristics of the selected studies

Study	country	Study type	N(Exp/Ctr)	Mean age	Duration of disease	ILL	rTMS protocol	Sex, women n(%)	Coil	Target spot	Outcomes index	Fo up
Tarig et al.2015	UK	C	10/16	38.8		IBS	600pulses×1h,10Hz, 80%rMT, M1,1h	90	8	M1		
Anne et al.2019	France	P	12	38 ± 8	9y	Endometriosis	1500pulses×5days, 10Hz,80%rMT, M1,4w	100	8	M1		1r
Cervigni et al.2018	Italy	C	7/6	52.6 ± 12.6	19.1 ± 9.4y	IBS	1500pulses×14days, 20Hz,110%rMT, M1,2W	100	H	M1		1.
Hodaj et al.2020	France	P	18	60.4 ± 15.9	7.83 ± 5.39y	Pudendal neuralgia	2000pulses×12days, 10Hz,80%rMT, rDLPFC,3W	72.2	8	rDLPFC		6r
Nikkola et al.2020	Finland	p	11	54.3 ± 15.9	9.2y	CP/CPPS	1500pulses×5days, 10Hz,110%rMT, M1,12W	0	8	M1		3r
Louppe et al. 2012	France	R	2	59.5	7.5y	Pelvic and Perineal pain	2000pulses×10days, 40Hz,80%rMT, M1,4W	100	N	M1		3v
C.Melchior et al.2014	France	C	8/9	44.0 ± 12.6	8.2 ± 6.8y	IBS	2000pulses×5days, 20Hz,80%rMT, M1,4W	52.3	N	M1		

P: parallel sham control; C: crossover sham control; R: case reports; Ctr: control group; Exp: experimental group; M: month W: week; D: day; N: Not recorded; IB irritable bowel syndrome; BPS: bladder pain syndrome; CP/CPPS: Chronic Prostatitis/Chronic Pelvic Pain Syndrome; visual analogue scale (VAS) 36-item Sh Term Health Survey (SF-36) Endometriosis Health Status Questionnaire (EHP-30) Beck's questionnaire Hospital Anxiety Scale and Depression (HAD) Nati Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) The Overactive Bladder Questionnaire (OAB-q)

Risk of Bias Assessment

Two of these articles [20, 23]reported a method for random sequence generation (Fig. 2). Five did not state whether randomization was concealed. The participants or research team were not blind in two surveys and the blind method was not mentioned in detail in two reports. In five studies, there was no explanation for blindness in the outcome assessment. Two studies had incomplete reporting of results, and two studies had missing follow-up and incomplete outcome data, with many deviations [15, 24].

Pain Intensity

Seven comparisons from the seven surveys involved pain intensity, all of which were meta-analyzed by all comparisons of the VAS pain scale, and the results showed that there was no significant change after treatment (n = 176, SMD = 0.18, 95% CI − 0.07 to 0.42, p = 0.15; I^2 = 75%; the fixed-effect model), and the results in one of the studies received experimental design impact, rTMS intervention was only one hour. And after excluding this study, the results of the six studies showed significant improvement in pain (n = 156, SMD = 1.48, 95% CI 0.8 to 2.16, p < 0.0001, I^2 = 62%; the effect Fig. 3, Fig. 4), Each study intervention was conducted for more than two weeks.

At the end of the course of follow-up, two out of seven studies had pain outcomes at one month of follow-up. At this point, it doesn't hold significance (SMD = 0.69, 95% CI − 0.22 to 1.60, I2 = 0.0%; Fig. 5).

Symptoms

Three studies reported the effects of rTMS on symptoms measured with the EPH-30 [26], NIH-CPSI [27], and OABq [28] in subjects with CPPS, the Endometriosis, CP/CPPS, and IBS Symptom Evaluation Scale. Therefore, due to the use of outcome measurement tools not used in the study, the results are incompatible, and the overall pooled analysis is not appropriate (Fig. 6).

Emotional effect

Two studies reported complete mood treatment results, using the Beck Scale [29] and the effects of rTMS measured by the HAMD [30] on anxiety versus depression in subjects, respectively (Fig. 7).

Quality of life

There are 4 articles mentioning the SF-36. Three of these studies recorded SF-36 [31] scores after treatment, and the control groups showed a large decrease (SMD, 8.69,95%CI, 12.04 to 5.35, I^2 = 3%; Fig. 8)

Subgroup Analysis

In five studies using an rTMS protocol with 80% rMT intensity, four repeated stimulus studies were extracted, they all had courses longer than 2 weeks, survey results (SMD = 1.39, 95% CI 0.64 to 2.14, I2 = 54%; Fig. 9). Two repeated stimulation studies with stimulation parameters of 110% rMT, the meta-analysis result was: (SMD = 1.89, 95% CI 0.26 to 3.51, I2 = 84%; Fig. 10), These studies were composed of high-frequency stimulation. Under the influence of the two stimulus parameters, the effectiveness of the difference was demonstrated. The confidence interval and heterogeneity of the high-intensity group were higher than those of the low-intensity group, which may be related to the difference in outcome calculation standards and case inclusion baseline. The meta-data of the two groups cannot directly prove that the high-intensity group is superior to the low-intensity group.

Discussion

We systematically reviewed seven clinical trials investigating the effects of rTMS on CPPS. Patients receiving repetitive rTMS had higher SF-36 scores and lower pain compared to controls. These effects lose significance at one month after the last treatment. In addition, there was no reduction in anxiety and depression, no reduction in various symptom scores, and a new non-significant correlation between pain severity and rTMS stimulation parameters.

We found that pain intensity, as measured by VAS scores, improved in repeated stimulation studies, and that improvement was also significant in a single case report [32] that was not included, but did not meet the inclusion criteria of the meta-analysis.

Considering that most of the articles had poor double-blind effect, the trial allocation was not randomized, and the resulting outcome measures were quite different. The heterogeneity of the results of this study is generally not applicable because the anxiety, depression and symptom evaluations cannot be globally evaluated because different measurement tools are used in each survey.

In our analysis, 7 studies included 6 on motor cortex[15, 20, 22–25] and only one on prefrontal cortex[21]. All seven studies analyzed used HF-rTMS as single or repetitive stimulation. Several studies have also confirmed the more significant effect of Hf-rTMS stimulation of the M1 region on chronic pain[33–36], and there are also systematic reviews[37] that have studied the effect of Hf-rTMS stimulation of the dorsolateral cortex prefrontal on chronic pain, and their studies have shown the short-term, mid-term and long-term analgesic effects of transcranial magnetic stimulation on neuropathic pain in the DLPFC. This is why the results of the follow-up period are presented in this article; however, due to the incomplete recording of data, there was no significant difference in pain intensity one month after the last treatment. A recent meta-analysis concluded that Hf-rTMS has therapeutic implications for the motor cortex for a variety of diseases, including not only chronic pain, but also depression and anxiety. In several studies [38, 39], symptom scores were not limited to the evaluation of the disease itself, but also included gastrointestinal function evaluation and urinary function evaluation. Therefore, the analysis of the results of this study used the pain score as the primary measure and also included mood, symptoms, and quality of life evaluations. However, the exact mechanism of action by which rTMS affects pain is unknown. The mechanism of labor pain in M1 and DLPFC [40] area by transcranial magnetic stimulation may involve direct inhibition of spinal transmission of nociceptive signals. A review has shown that rTMS of prominent axons and local interneurons activated at high frequencies (10 or 20 Hz) has established that cumulative pain can be reduced for at least a few weeks after 10 consecutive working days; the pain-reducing effect of transcranial magnetic stimulation is also considered to be mediated through subcortical neural networks and is the result of enhancement of the dopamine-opioid system, and it has also been reported that transcranial magnetic stimulation therapy can increase serum-endorphin concentrations[16, 19, 34].

In the study, through the analysis of stimulation parameters, all studies were high-frequency stimulation, of which the intensity was 110% rMT in two studies and 80% rMT in five studies. There were very few studies comparing the stimulation intensity, but some studies [] had shown that different intensities would have an effect. The study by Zheng et al. [41] showed that rTMS had a more significant effect on cerebral blood flow at high intensity, and the intensity effect was greater than the frequency effect. However, in the results of this meta-analysis, the 95% confidence interval of the high-intensity group was larger than that of the low-intensity group, the difference was not significant, and the pain intensity of the experimental group was reduced after repeated stimulation. However, it cannot be stated that the strength has no effect on the difference in the results, mainly because the included article is not a randomized controlled trial with a strictly designed protocol.

In particular, the results of this article include two studies of the relationship between pain and bowel sensation during transcranial magnetic stimulation, one study measured rectal and anal pain and sensory thresholds, and concluded that rTMS at 10 Hz appears to mainly change anal and rectal pain with little effect on anorectal sensation, and the other study concluded that transcranial magnetic stimulation of the primary motor cortex improves maximum rectal tolerance in IBS patients with significant allergy. Both of them provide a basis for IBS in neurostimulation therapy and also lay the foundation for the improvement of CPPS in terms of gastrointestinal conditions.

Two studies reported mild and transient headache, nausea, inappropriate site of stimulation, and some neurobehavioral adverse events, which were common adverse reactions to TMS and resolved spontaneously in a short period of time. There were no serious adverse events reported, and the serious adverse event of transcranial magnetic stimulation was epilepsy, which was not observed in this study.

The strengths of our study lie in several aspects. First, we present the first extensive summary of rTMS for the treatment of this disorder in CPPS. Secondly, for the first time, the comparative analysis of rTMS in the treatment of CPPS under different intensity stimulation parameters; third, we included the latest clinical trial articles, providing a reference basis for subsequent treatment and research.

The present meta-analysis also has several limitations. First, the number of participants in all included studies was small, and patients' demographics, study design, and stimulation parameters were heterogeneous. Second, all included studies had a female preponderance. Although no correlation between treatment effect and gender was found in the meta-analysis, in fact, the incidence of CPPS in men was not low, but their study was biased towards medical and surgical treatment. Third, the diagnostic inclusion and evaluation criteria used were different. CPPS contains diverse diseases, and three studies are the same studies but their symptom diagnosis and classification are not the same. Fourth, most of the included surveys allowed concurrent medication and other treatments during the study period. Therefore, the majority of transcranial magnetic stimulation is used as an adjuvant therapy, and the results receive interactions between drugs and other treatments, and the effectiveness of rTMS alone needs further validation. Fifth, due to insufficient data and high heterogeneity among studies, we failed to complete the group analysis of stimulus flapping, adjuvant therapy for participants, its relationship with symptom improvement, and adverse effects. However, these results are important for assessing the treatment of chronic pain[42], and a large number of trials are needed in the future to confirm the results in this regard. Finally, although no serious adverse events were reported, the relatively small number of participants in most studies may have affected the accident rate and needs to be illustrated by studies based on large samples for a long time with a single disease.

Future research in this field should still be the focus, and many trials with more perfect standards are needed. For example, the CPPS diagnostic criteria and treatment recommendations of the EUA guidelines[7] are uniformly used; based on a reasonable and statistically significant sample size, a more objective randomized design trial is conducted; it is recommended to use the CPPS pain and urinary symptom scoring scale, and use the male and female CPPS measurement tools recommended by the specifications according to gender differences; and there is also a great need for mechanistic studies, both from cortical mechanisms and from peripheral mechanisms.

Conclusions

This meta-analysis revealed that rTMS is safe and effective for treating multiple domains of CPPS but has no significant effects on symptoms or emotional aspects. It may be due to improper experimental design and too little research data. Therefore, larger scale trials using more rigorously designed and standardized training protocols are still needed to demonstrate in investigating the future of repetitive transcranial magnetic stimulation for chronic pelvic pain syndrome.

Declarations

Declarations of interest

This review has no financial or non-financial support.

Competing interests

The authors declare no competing interests.

Data availability statements

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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42. Patel, K.V., et al., Clinical outcome assessment in clinical trials of chronic pain treatments. Pain Rep, 2021. **6**(1): p. e784.

Figures

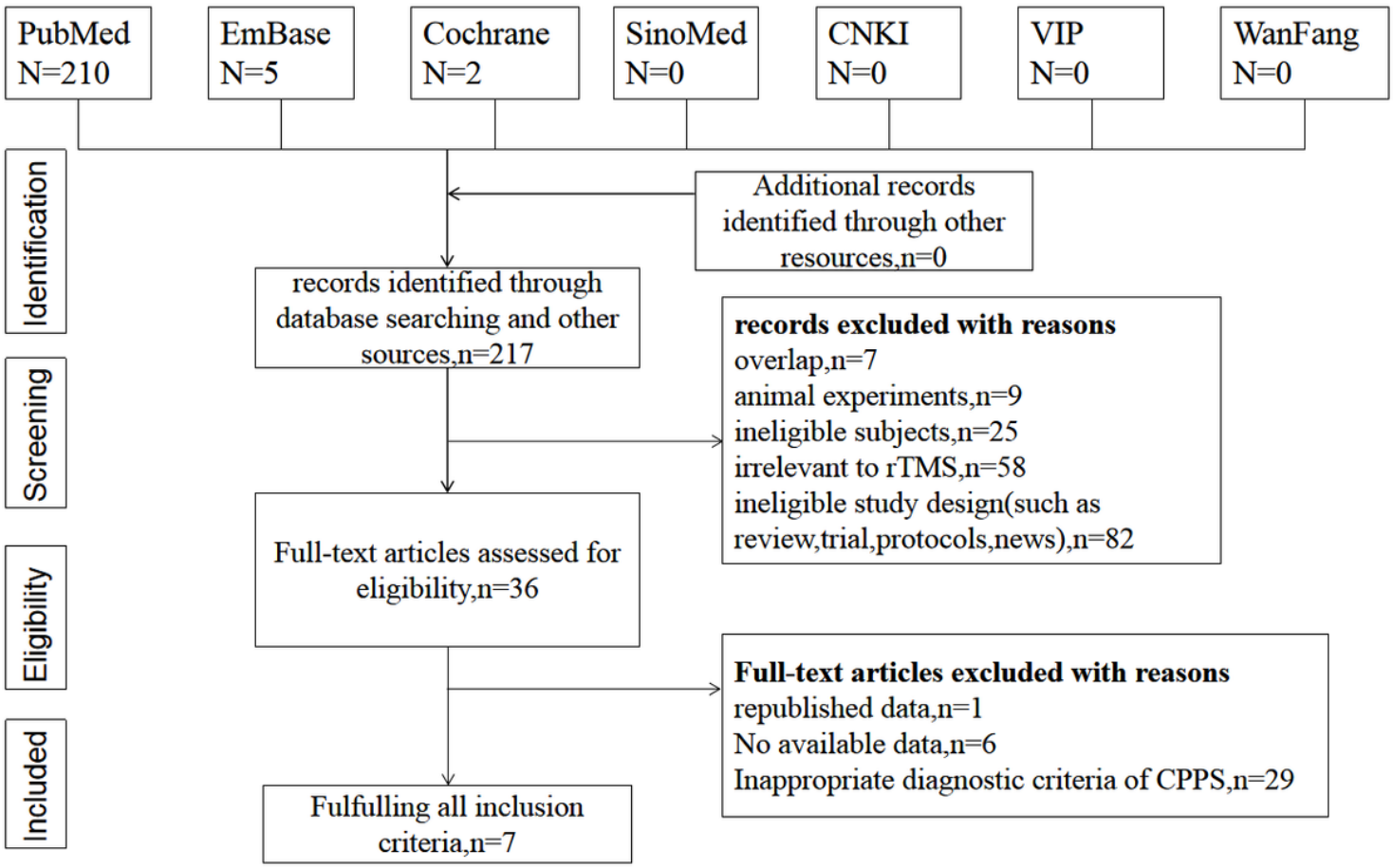

Figure 1

Literature screening process and results.

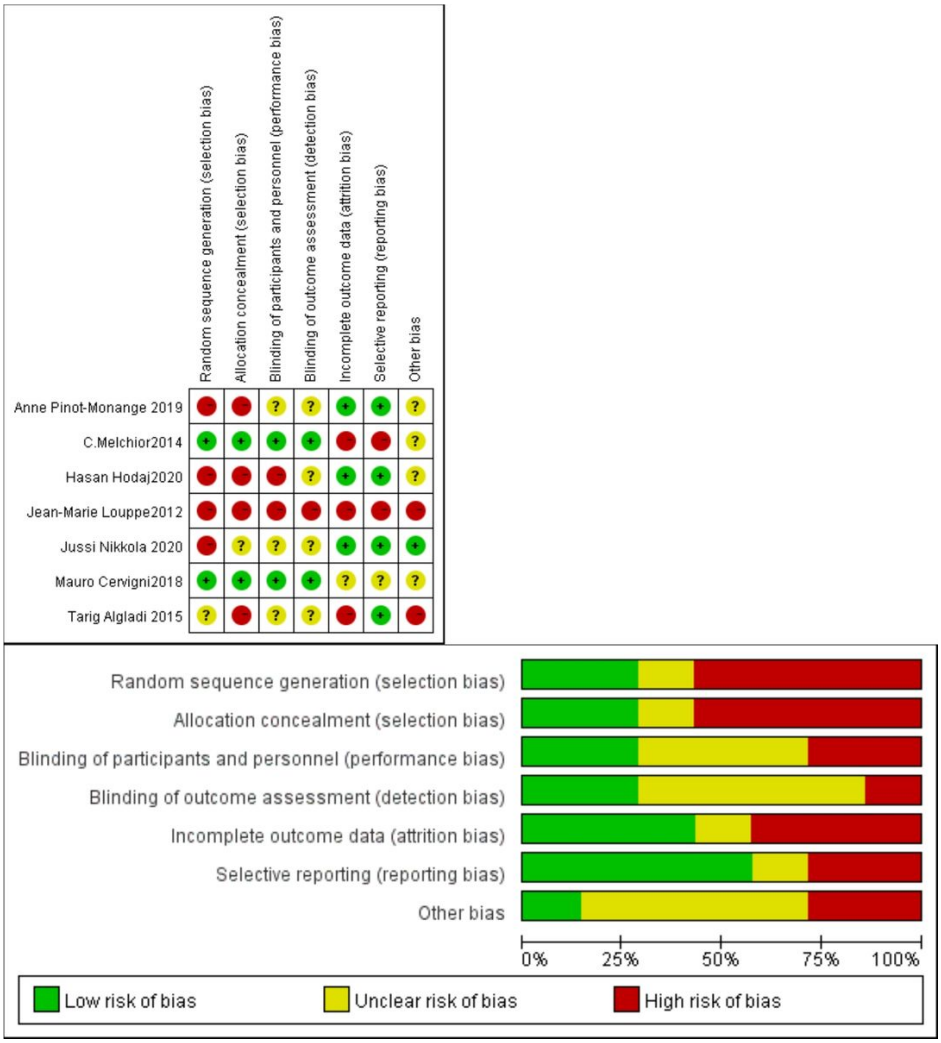

Figure 2

Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

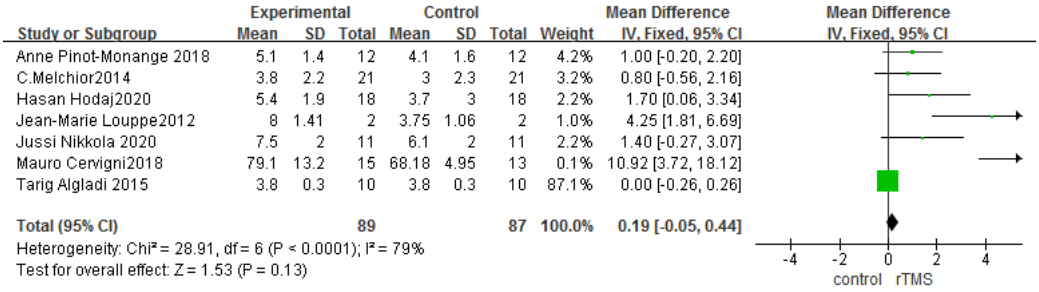

Figure 3

Forest plot of standardized mean differences in VAS pain questionnaire after treatment. Squares indicate effect sizes of individual studies, lines indicate 95% CI, and diamond indicates the summarized effect size.

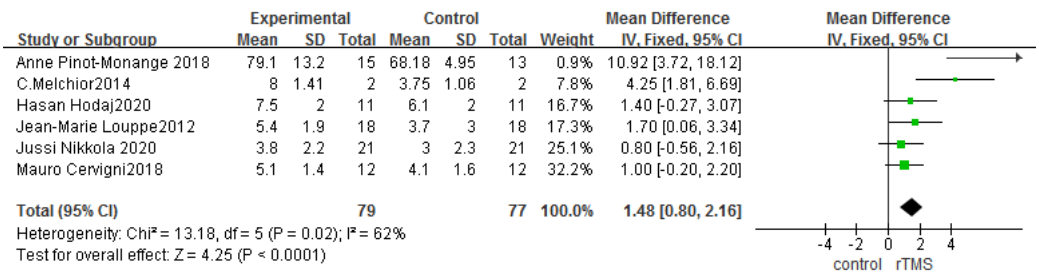

Figure 4

Forest plot of the standardized mean difference of VAS pain questionnaire after long-term treatment. Squares indicate effect sizes of individual studies, lines indicate 95% CI, and diamond indicates the summarized effect size.

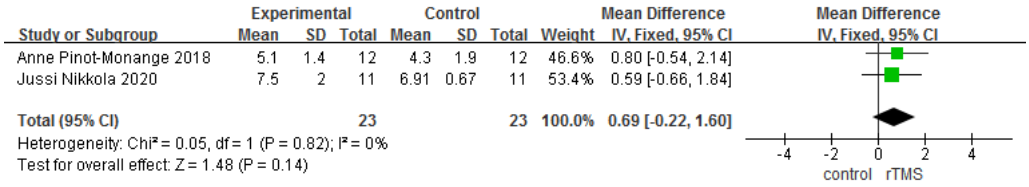

Figure 5

Forest plot of the standardized mean difference of VAS pain questionnaire of follow-up. Squares indicate effect sizes of individual studies, lines indicate 95% CI, and diamond indicates the summarized effect size.

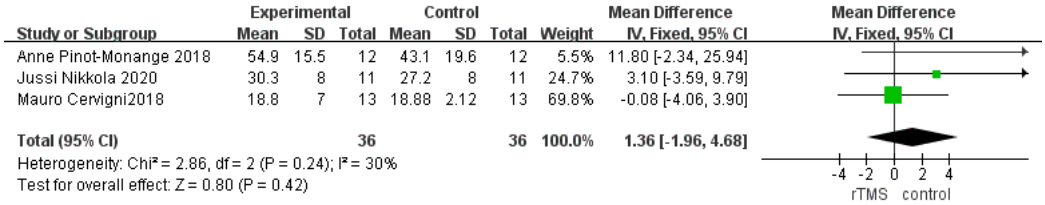

Figure 6

Forest plot of the standardized mean difference of symptoms after treatment. Squares indicate effect sizes of individual studies, lines indicate 95% CI, and diamond indicates the summarized effect size.

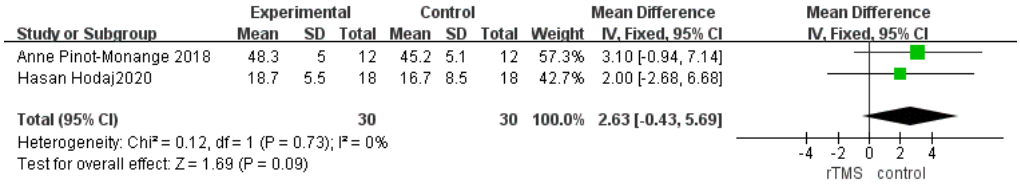

Figure 7

Forest plot of the standardized mean difference of anxiety and depression after treatment. Squares indicate effect sizes of individual studies, lines indicate 95% CI, and diamond indicates the summarized effect size.

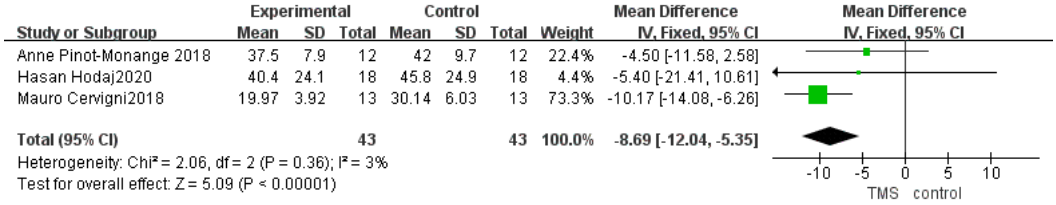

Figure 8

Forest plot of the standardized mean difference of SF-36 questionnaire after treatment. Squares indicate effect sizes of individual studies, lines indicate 95% CI, and diamond indicates the summarized effect size.

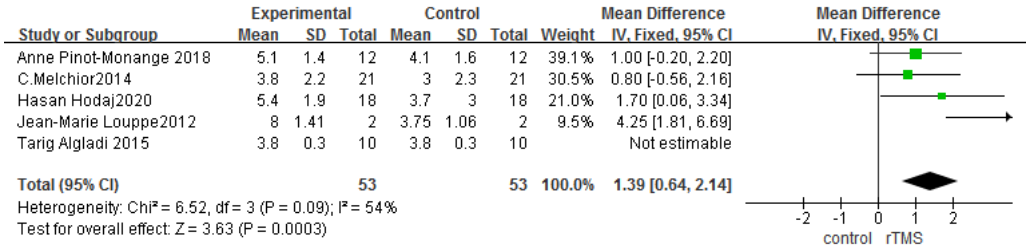

Figure 9

Forest plot of the effect of rTMS at 80% rMT on participants. Squares indicate effect sizes of individual studies, lines indicate 95% CI, and diamond indicates the summarized effect size.

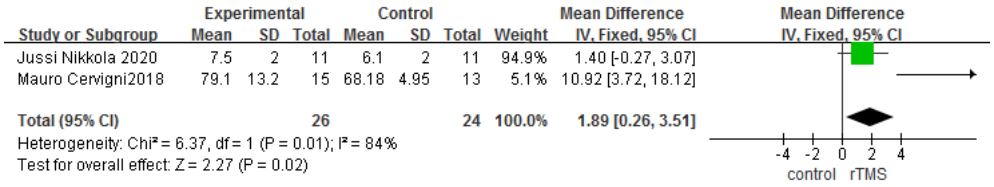

Figure 10

Forest plot of the effect of rTMS at 110% rMT on participants. Squares indicate effect sizes of individual studies, lines indicate 95% CI, and diamond indicates the summarized effect size.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMA2020checklist.docx