Systematic Review and Meta-Analysis

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Effect of non-invasive brain stimulation on neuropathic pain following spinal cord injury

A systematic review and meta-analysis

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Abstract

Background: In recent years, some studies indicated that repetitive transcranial magnetic stimulation (rTMS) could relieve neuropathic pain (NP) following a spinal cord injury (SCI), whereas some studies showed no pain relief effect. In addition, some studies showed the analgesic effect of transcranial direct current stimulation (tDCS) on NP post SCI, whereas other studies showed no effect.

Methods: We systematically searched on the PubMed, Web of Science, EMBASE, Medline, Google Scholar for studies exploring the analgesic effect of rTMS or tDCS on NP post SCI until November 2019. Meta-analysis was conducted to summarize results of these studies.

Results: The present quantitative meta-analysis indicated no significant difference in the effect of treatment on NP following SCI between rTMS and sham rTMS over the motor cortex at about 1 week after the end of the rTMS period (standardized mean difference (SMD) = 2.89, 95% confidence interval (CI) = −0.27 to 6.04). However, the study indicated that rTMS showed significantly better pain relief of treatment compared with sham rTMS between 2 and 6 weeks after the end of the rTMS period (SMD = 3.81, 95%CI: 0.80–7.52). However, no sufficient evidence could be provided to make a meta-analysis for the analgesic effect of tDCS on NP following SCI over the primary motor area (M1).

Conclusions: In conclusion, the present meta-analysis suggested that rTMS did not show early analgesic effect on NP after SCI, but showed better middle-term analgesic effect, compared with sham rTMS. More large scale, blinded randomized controlled trials (RCTs) were needed to explore the analgesic effect of rTMS and tDCS on NP following SCI.

Abbreviations: CI = confidence interval, CNS = central nervous system, FDG-PET = fluorodeoxyglucose positron emission tomography, M1 = primary motor area, NIBS = non-invasive brain stimulation, NP = neuropathic pain, NRS = numeric rating scale, PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analysis, RCTs = randomized controlled trials, rTMS = repetitive transcranial magnetic stimulation, SCI = spinal cord injury, SD = standard deviation, SMD = standardized mean difference, tDCS = transcranial direct current stimulation, VAS = visual analogue scale.

Keywords: neuropathic pain, repetitive transcranial magnetic stimulation, spinal cord injury, transcranial direct current stimulation

1. Introduction

Spinal cord injury (SCI) is one of the most serious injuries because of a traumatic or non-traumatic event and results in sensory, motor, or autonomic dysfunction. It finally influences patients' physical, psychological, and social function.[1] Epidemiological evidence reported the incidence of SCI as 10.5 cases per 100,000 people.[2] Chronic pain is a common secondary complication of SCI with a prevalence of 61%.[3] Pain might result in

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

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depression,[4] sleep disturbances,[5] and reduced quality of life.[4] Neuropathic pain (NP) is regarded as the most severe pain post SCI and located at or below the level of injury.[6] According to randomized controlled trials, pregabalin is regarded as the most effective drug for the treatment of SCI.[7] A meta-analysis of randomized controlled trials indicated that pregabalin was effective in reducing pain, depression, and anxiety of SCI patients.[8] However, treatment with pregabalin might increase the risks of weight gain, dizziness, vertigo, somnolence, peripheral oedema, fatigue, visual disturbances, ataxia, non-peripheral oedema, and euphoria.[8] Accumulating evidence showed that NP post SCI is related to functional reorganization of central nervous system (CNS) activity and hyperexcitability of the somatosensory and motor cortices.[9] According to previous studies, brain stimulation could affect brain plasticity and might be valuable for the treatment of chronic pain.[9] At present, there are 2 well-known, safe, commonly used, non-invasive brain stimulation (NIBS) techniques, including transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). Increasing evidence showed that repetitive transcranial magnetic stimulation (rTMS) could partially and transiently relieve pain in healthy participants in chronic pain conditions.[10] It is also reported that tDCS, applied over the sensory-motor cortex, could reduce pain sensation in healthy participants.[11] In recent years, some studies indicated that rTMS could relieve NP following SCI, whereas some studies did not.[12] In addition, some studies showed the analgesic effect of tDCS on NP post SCI, whereas other studies showed no effect. In this study, we aimed to make a systematic review and meta-analysis to evaluate effect of non-invasive brain stimulation (including rTMS and tDCS) on NP following SCI.

2. Methods

2.1. Search strategy

Ethical approval was not applicable in the study. According to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guideline,[13] a meta-analysis was conducted to explore the effect of non-invasive brain stimulation on NP following SCI. Electronic databases (PubMed, Web of Science, EMBASE, Medline, Google Scholar) were used to search for articles until November 2019. We used terms with following keywords: ("transcranial magnetic stimulation" OR "TMS" OR "transcranial direct current stimulation" OR "tDCS") AND ("spinal injury") AND ("pain").

2.2. Inclusion criteria and exclusion criteria

Only randomized controlled trials (RCTs), crossover RCTs, and high-quality comparative studies were included in the present study. These studies showed sufficient data for the comparison of pre- and post-treatment visual analogue scale (VAS) or numeric rating scale (NRS) scores between 2 groups of SCI patients given non-invasive brain stimulation versus sham stimulations. In this step, we excluded following articles:

(1) studies which did not focus on non-invasive brain stimulation and SCI;
(2) reviews, meta-analysis, and case studies.

After that, full texts were read to exclude articles which did not provide sufficient information of pre- and post-treatment VAS or numeric rating scale (NRS) scores.

2.3. Data collection

We extracted data as follows: authors and publication year, research location, numbers of cases and controls, research type, mean ages of cases and controls, gender, research type, interventions, damage location, and duration of injury.

2.4. Meta-analysis

All analyses were conducted using STATA 12.0 software. The mean values and standard deviation (SD) of reduction rate of pain scores were obtained or calculated from the included studies. Heterogeneity between studies was assessed with Cochran Q test and I^2 method. A fixed effects model was performed when the threshold ($I^2 < 50\%$) for heterogeneity was not reached. Inversely, a random effects model was used when the threshold for heterogeneity was exceeded. Quality appraisal was conducted using the Cochrane Risk of Bias Tool. Data were analyzed using Review Manager 5.3.

3. Results

3.1. Search results

Figure 1 illustrates the procedures of inclusion and gradual exclusion. Supplementary Table 1, http://links.lww.com/MD/E713 showed characteristics of included studies. Two independent reviewers screened the titles and abstracts for eligibility. Finally, the study included 6 and 4 articles for rTMS[12,14–18] and tDCS,[19–22] respectively. Studies for rTMS included 2 RCTs and 4 crossover RCTs. These studies totally included 62 SCI patients given rTMS and 65 patients given sham rTMS over motor cortex. In addition, studies for tDCS included 4 crossover RCTs. These studies totally included 46 SCI patients given tDCS and 41 patients given sham tDCS.

3.2. Meta-analysis results and systematic review

There were 6 studies included for effect of rTMS over the motor cortex on NP following SCI. A study was not included in meta-analysis because the study showed only immediate effect of rTMS on NP.[17] The present quantitative meta-analysis indicated no significant difference in the effect of treatment on NP following SCI between rTMS and sham rTMS at about 1 week after the end of the rTMS period (standardized mean difference (SMD) = 2.89, 95% confidence interval (CI) = −0.27 to 6.04, Fig. 2). However, the study indicated that rTMS showed significantly better pain relief effect of treatment compared to sham rTMS between 2 and 6 weeks after the end of the rTMS period (SMD = 3.81, 95%CI: 0.80–7.52, Fig. 3). Additionally, significant heterogeneities were indicated among these included studies. Yilmaz et al[14] indicated that early pain relief of rTMS on NP following SCI was not superior to sham rTMS, whereas rTMS showed better middle-term (over and equal to 6 weeks) analgesic effect compared with sham rTMS. In addition, Kang et al[12] showed no significant difference in changes of average NRS scores from baseline to 1 week, 3 weeks, 5 weeks, and 7 weeks after the end of the rTMS period between rTMS and sham stimulation. Jette et al[15] indicated no significant difference in reduction rate of NRS from baseline to 5 to 6 days after the end of the rTMS period between rTMS and sham rTMS. Defrin et al[16] showed no significant difference in reduction rate of VAS from baseline to 4.5 weeks after the end of the rTMS period between rTMS and sham rTMS.

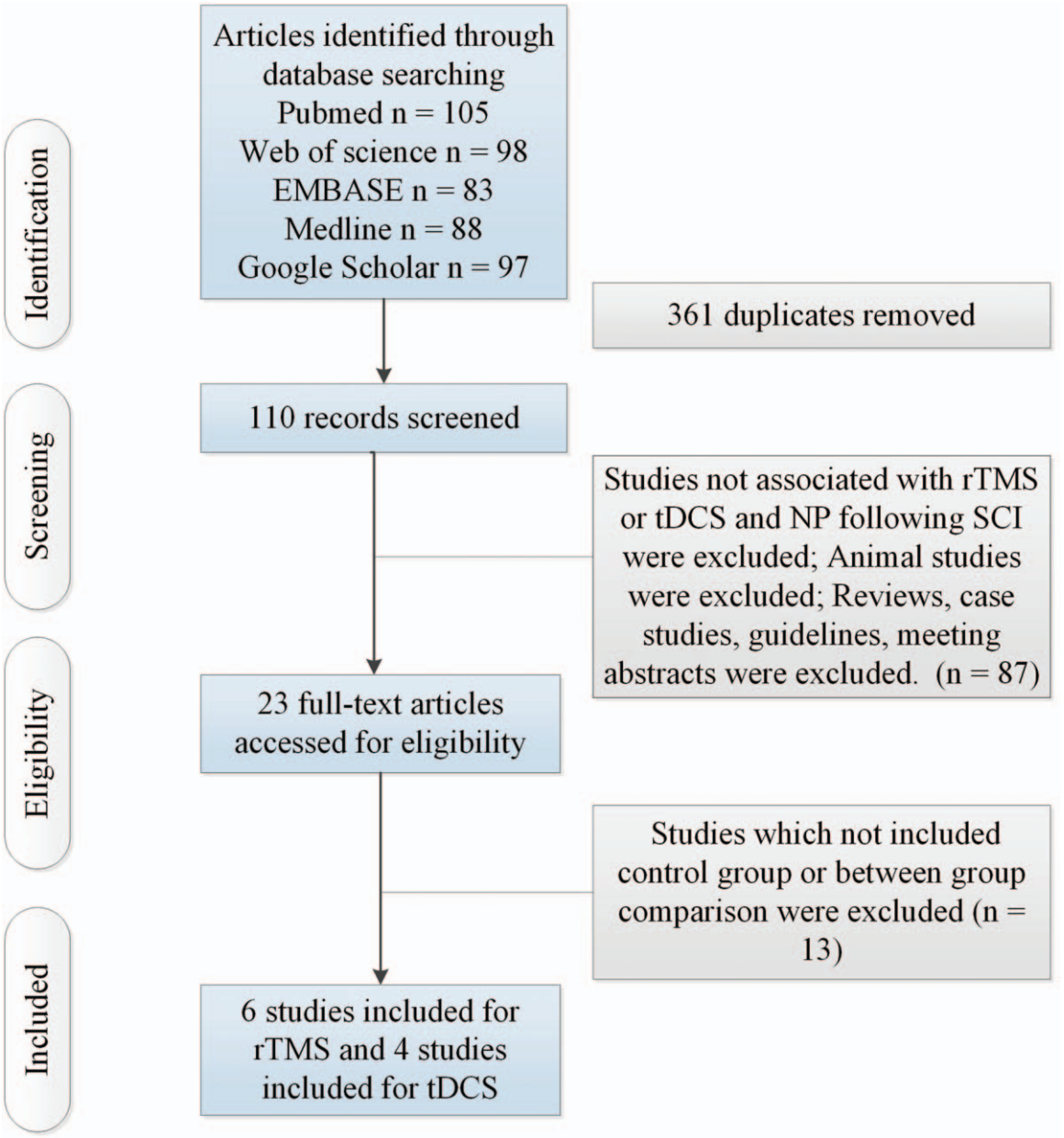

Figure 1. Characteristics of studies included in the meta-analysis for the analgesic effect of rTMS and tDCS on NP following SCI. NP, neuropathic pain; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation.

In addition, Lefaucheur et al[18] indicated that rTMS over motor cortex lead to a significant relief of chronic pain post SCI.

There were 4 studies included for effect of tDCS over the primary motor area (M1) on NP following SCI. The 4 studies explored differences in analgesic effect of tDCS at different time-points after the end of the tDCS period. Thus, no meta-analysis was made to summary results of these studies. Ngernyam et al[19] indicated anodal tDCS (2 mA) over the left M1 for 20 min resulted in significant reduction in pain intensity following SCI at 2 days after the end of the tDCS period, compared with sham tDCS. However, Wrigley et al[20] indicated no significant difference in changes of NRS scores from baseline to 4 weeks after the end of 5 tDCS treatment period between anodal and sham tDCS. Soler et al[22] indicated no significant differences in analgesic effect on NP following SCI at 2 and 12 weeks after the end of the tDCS period between tDCS and sham tDCS. Fregni et al[21] showed that tDCS showed a better analgesic effect on NP post SCI at 2, 3, 4, and 5 days after the end of the tDCS period, compared to sham tDCS, whereas no significant differences in analgesic effect were detected between tDCS and sham tDCS at the 16 days after the end of the tDCS period.

The risk of bias graph is shown in supplementary Figure 1, http://links.lww.com/MD/E711. Details of the risk of bias summary can be found in supplementary Figure 2, http://links.lww.com/MD/E712.

4. Discussion

The present study indicated that early analgesic effect of rTMS over the motor cortex on NP post SCI was not superior to sham

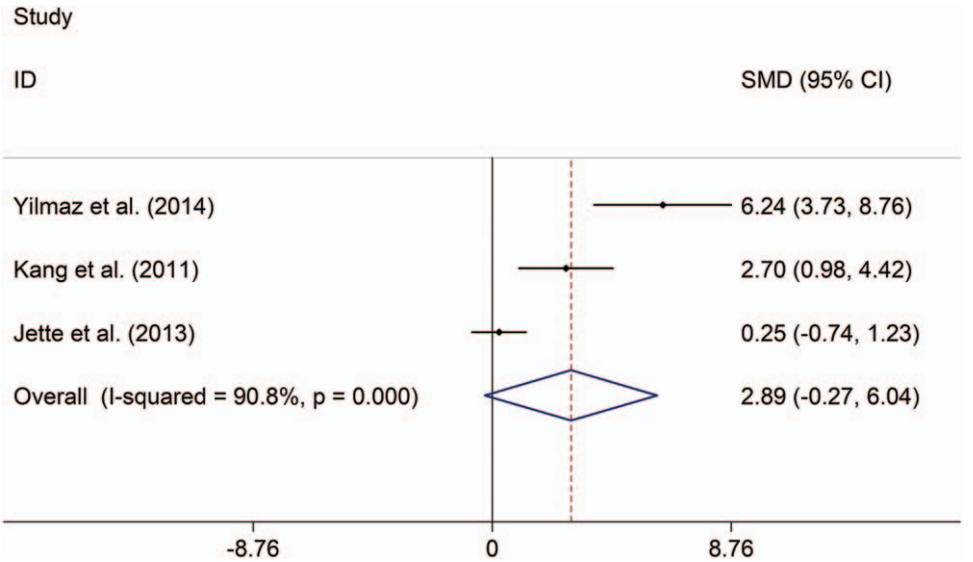

Figure 2. Forest plot for ratios of pain scores changes in patients who received rTMS and sham rTMS interventions from baseline to about 1 wk after the end of the rTMS period. rTMS, repetitive transcranial magnetic stimulation; SMD, standardized mean difference.

rTMS, whereas rTMS showed better middle-term analgesic effect, compared with sham rTMS. However, no sufficient evidence could be provided to make a meta-analysis for the analgesic effect of tDCS on NP following SCI over the M1.

Up to now, high-frequency (a frequency between 5 and 20 Hz) rTMS over the motor cortex has been confirmed as a valuable intervention to relieve NP.[23,24] In the past 1 decade, some researchers explored the mechanisms of the analgesic effects of rTMS over the motor cortex in NP patients.[25,26] Some studies indicated that stimulation over the motor cortex could regulate neural activity in pain networks.[27] Furthermore, the stimulation could modulate nociceptive inhibitory control regions locally and in remote brain regions, eventually result in pain relief.[28,29] Additionally, the analgesic effects might be associated with modulations of complex opioidergic, glutamatergic, or gabaergic neurotransmitter systems.[30,31] In the past 1 decade, some systematic review and meta-analysis studies payed attention to physiotherapy intervention for NP. A Cochrane review reported by Louise et al indicated that high-frequency rTMS of the motor cortex might show short-term analgesic effects on NP following SCI.[24] In addition, that study indicated that low-frequency rTMS over the dorsolateral prefrontal cortex did not show any analgesic effects on NP following SCI.[24] A Cochrane review reported by Boldt et al indicated that rTMS showed no analgesic

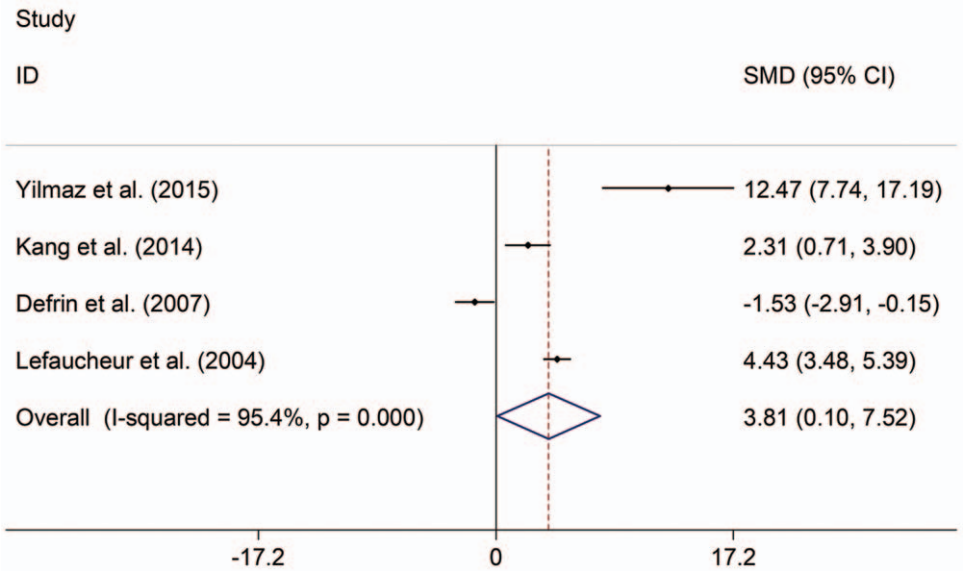

Figure 3. Forest plot for ratios of pain scores changes in patients who received rTMS and sham rTMS interventions from baseline to 2 to 6 wk after the end of the rTMS period. rTMS, repetitive transcranial magnetic stimulation; SMD, standardized mean difference.

effects on NP in people living with SCI.[32] Albert et al made a meta-analysis showing that high-frequency rTMS was effective in suppressing NP.[33] Another meta-analysis made by Jin et al indicated that high-frequency rTMS stimulation over the motor cortex was effective in relieving NP. In addition, the authors showed that the analgesic effects of rTMS treatment might be continued for at least 1 month.[34] The present study showed that early analgesic effect of rTMS over the motor cortex on NP post SCI was not superior to sham rTMS, whereas rTMS showed better middle-term analgesic effect, compared with sham rTMS. The present study was the first study exploring the short- and middle-term analgesic effects, respectively. The result provided an objective evidence to the middle-term analgesic effects of rTMS over the motor cortex on NP following SCI.

No sufficient evidence could be provided to make a meta-analysis for the analgesic effect of tDCS on NP following SCI over the M1 in the present study. The analgesic effects of M1 stimulation might be associated with inhibitions of spinal transmission of nociceptive signals.[35] The association between stimulation over the M1 and NP relief is not obvious firstly, M1 might be an entry door into a larger network associated with the modulation of NP.[28] Yoon et al indicated that the treatment with tDCS over the motor cortex for NP post SCI could modulate cognitive and emotional components of NP, and normalize excessive attention to NP and NP-related information using [(18) F]-fluorodeoxyglucose positron emission tomography ([(18)F] FDG-PET).[36] Mehta et al indicated a moderate effect of tDCS in reducing NP following SCI; but the effect could not be maintained at follow-up points with a meta-analysis.[28] That study did not explore the short- and middle-term analgesic effect of tDCS, respectively. Previous studies indicated that the level of evidence remains higher for rTMS than tDCS due to the efficacy of non-invasive M1 stimulation in NP.[37,38]

The study had some limitations. In meta-analysis for analgesic effects of rTMS over the motor cortex on NP post SCI, the amount of included studies was limited to explore the sources of heterogeneities. In addition, in meta-analysis for analgesic effects of tDCS over the M1 on NP post SCI, the amount of included studies was limited to explore the short- and middle-term analgesic effect of tDCS, respectively.

In conclusion, the present meta-analysis suggested that rTMS did not show early analgesic effect on NP after SCI, but showed better middle-term analgesic effect, compared to sham rTMS. More large scale, blinded RCTs should be made to explore the analgesic effect of rTMS and tDCS on NP following SCI.

Author contributions

Zhubin Shen participated in the drafting of the manuscript, acquisition of data, analysis and interpretation of the data and statistical analysis. Zhongrun Li participated in acquisition of data, analysis and interpretation of the data, statistical analysis. Junran Ke participated in acquisition of data. Changhao He participated in acquisition of data. Din Zhang participated in acquisition of data. Zhiming Liu participated in acquisition of data. Zhili Zhang participated in analysis and interpretation of the data. Anpei Li participated in analysis and interpretation of the data. Shuang Yang participated in proof of the manuscript. Xiaolong Li participated in proof of the manuscript. Ran Li participated in proof of the manuscript. Kunchi Zhao participated in proof of the manuscript. Qing Ruan participated in proof of the manuscript. Haiying Du participated in proof of the manuscript. Li Guo participated in participated in obtaining funding, conception and design of the research, critical revision of the manuscript for important intellectual content. Fei Yin participated in obtaining funding, conception and design of the research, critical revision of the manuscript for important intellectual content.

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