INPLASY PROTOCOL

An update meta-analysis of rTMS on patient with fibromyalgia: recommendation or not?

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Review Stage at time of this submission: **The review has not yet started.**

Conflicts of interest:
None.

Sun, P[1]; Fang, L[2]; Liu, Y[3]; Qi, R[4].

Review question / Objective: **Although there had meta-analyses in the past, the efficacy of rTMS on fibromyalgia is still controversial and conflicting. Therefore, is rTMS recommend for fibromyalgia treatment or not is a key question for clinical rehabilitation.**
Condition being studied: **The fibromyalgia syndrome is a rheumatic disease with a prevalence of 2.7% worldwide. Pain is a feature and sometimes the subjective symptoms of fibromyalgia syndrome. The secondary symptoms is fatigue, insomnia and further disorders such as depression and anxiety. As a non-invasive brain stimulation approaches developed in recent decades, rTMS (Repetitive transcranial magnetic stimulation) can regulate the activity of cortical area thereby modulate functions and feelings of human body. Growing studies were performed to reveal the efficacy of rTMS on fibromyalgia syndrome. However, the effect of rTMS on the fibromyalgia syndrome is not uncovered and the controversy still exists. A systematic review and meta-analysis included 5 trials up to April 2014 demonstrated the superior effect compared with sham therapy on the life quality of patients with fibromyalgia syndrome. However, after adding 2 trails, a literature included 7 trials up to April 2016 showed that rTMS is not more effective than sham in reducing the severity of pain in patients with fibromyalgia, and the conventional recommendation of rTMS in the treatment of fibromyalgia is questioned. Up to date, some new trials emerged from last 5 years and demonstrated different effects of TMS on fibromyalgia syndrome.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 30 August 2020 and was last updated on 30 August 2020 (registration number INPLASY202080124).

INTRODUCTION

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prevalence of 2.7% worldwide. Pain is a feature and sometimes the subjective symptoms of fibromyalgia syndrome. The secondary symptoms is fatigue, insomnia and further disorders such as depression and anxiety. As a non-invasive brain stimulation approaches developed in recent decades, rTMS (Repetitive transcranial magnetic stimulation) can regulate the activity of cortical area thereby modulate functions and feelings of human body. Growing studies were performed to reveal the efficacy of rTMS on fibromyalgia syndrome. However, the effect of rTMS on the fibromyalgia syndrome is not uncovered and the controversy still exists. A systematic review and meta-analysis included 5 trials up to April 2014 demonstrated the superior effect compared with sham therapy on the life quality of patients with fibromyalgia syndrome. However, after adding 2 trails, a literature included 7 trials up to April 2016 showed that rTMS is not more effective than sham in reducing the severity of pain in patients with fibromyalgia, and the conventional recommendation of rTMS in the treatment of fibromyalgia is questioned. Up to date, some new trials emerged from last 5 years and demonstrated different effects of TMS on fibromyalgia syndrome.

METHODS

Search strategy: Search strategy for Pubmed for example: #1. Transcranial Magnetic Stimulation [Mesh] #2. Transcranial Magnetic Stimulation tl, ab #3. Magnetic Stimulation, Transcranial tl, ab #4. TMS tl, ab #5. 1 OR 2 OR 3 OR 4 #6. Fibromyalgia [MeSH] #7. Fibromyalgia OR FM OR FMS OR Fibrositis tl, ab #8. 6 OR 7 #9. 5 AND 8 #10. Randomized Controlled Trials OR trial OR placebo OR groups OR control OR Random* tl, ab #11. 9 AND 10.

Participant or population: Subjects with diagnosis of fibromyalgia.

Intervention: rTMS (Repetitive transcranial magnetic stimulation).

Comparator: Sham rTMS.

Study designs to be included: RCT.

Eligibility criteria: (1) Non-randomized controlled trial, before and after, interrupted time series, cross-over trail), observational studies (prospective and retrospective), case reports, reviews or systematic literature reviews and qualitative studies, opinion pieces, editorials, comments, news, letters. (2) Sufficient data concerning outcomes cannot be derived from study and authors cannot provide further help. (3) The rTMS is not the primary focus of the intervention. (4) The pain is a combined pain such as chronic pain combined of fibromyalgia, cancer pain and multiple sclerosis pain.

Information sources: These electronic databases were researched: Pubmed, the Cochrane Library, Exceerpta Medica Database (EMBASE), Web of Science, Physiotherapy evidence database. Language was limited to English. Databases were retrieved from the earliest data available to 2020/8/30. The references of previous literatures concerning rTMS on fibromyalgia were tracked carefully. The http://www.clinicaltrial.gov was searched for potential studies which is conducting or planed.

Main outcome(s): NPRS (Numerical pain rating scale) which reflects the pain intensity.

Additional outcome(s): The depression, anxiety index and quality of life index.

Data management: Data will be extracted by two independent reviewers (YL and RQ): Title; Place of publication country); Year of publication; Author information; Population (Age, gender, occupation); Setting; Methods (Coil, location, frequency, intensity, duration and follow-up); Results (Scores of pain, anxiety, depression, quality of life, etc. before and after TMS treatment). If data were missing or incomplete, we will try to contact authors by email to ask for original research data. Disagreements about study inclusion and extracted data were solved by consensus. If disagreements persisted, then consulted

by a third review expert. The data such as mean, SE and SD value from the literatures will be extracted. If the data are missing, expressed in the form of graph or difference before and after treatment, we will try to contact the author to provide the original data and calculation will be performed on the original data firstly. In the case that the above method is not available, digital rule software (engauge digitizer 7.2) will be employed to exclude the data of the graph in the literature.

Quality assessment / Risk of bias analysis: Quality Assessment: The Physiotherapy Evidence Database (PEDro) will be used to assess the quality of included articles as TMS is a type of physiotherapy. The methodological criteria were scored as: Yes (one point), No (zero points) or Don't know (zero points). The PEDro score of each selected study provided an indicator of the methodological quality (9–10=excellent; 6–8=good; 4–5=fair; <4=poor). Risk of bias: Two review authors will independently assess the risk of bias in included studies according to the criteria in the Cochrane Handbook for Systematic Reviews of Interventions as follows: the random sequence generation, allocation concealment, incomplete outcome data, blinding (participants, personnel, and outcome assessment), selective reporting, and other biases. After that, another two review authors will independently judged each study as having bias, a high risk of bias, or an unclear risk of bias.

Strategy of data synthesis: Review Manager (Revman, Version 5.3) software provided by the Cochrane Collaboration will be used for data analysis. For continuous variables, standardized mean difference (SMD) and 95% confidence interval (CI) will be used for statistics. The heterogeneity tests of each outcome will be performed using Chi-squared test and I2 statistic. When no significant heterogeneity was observed (I2 < 50%), the fixed-effects model will be used to perform meta-analysis. When heterogeneity was detected (P < 0.05 and I2 ≥ 50%), a random-effects model will be used. Funnel plots will be planned to visually investigate the asymmetry and potential publication bias along with the quantitatively Egger test. The subgroup and sensitivity analyses will also planned to explore possible reasons for statistical heterogeneity when I2>50%.

Subgroup analysis: If available, subgroup analyses will be performed following below items in our plan: type of rTMS (High frequency or low frequency, low intensity or high intensity), male/female of subjects, location of study, duration of treatment.

Sensibility analysis: The sensitivity analysis will be employed to investigate the influence of each study in the main outcomes using remove one at a time. Meta-regression will also be planned.

Language: Language will be limited to English.

Country(ies) involved: P.R.China.

Other relevant information: None.

Keywords: Transcranial magnetic stimulation; Fibromyalgia; Meta-analysis.

Contributions of each author:
Author 1 - Pingping Sun - Literature searching, quality assessment and Wring the manuscript.
Author 2 - Lei Fang - Literature searching and quality assessment.
Author 3 - Yang Liu - Data extraction.
Author 4 - Rui Qi - Study design, literature searching, quality assessment, modifing the manuscript, final approval for submission.