

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

Title (Provisional)

Repetitive Transcranial Magnetic Stimulation as An Adjunct to Quadriceps Strengthening Exercise in Knee Osteoarthritis: A Pilot Randomised Controlled Trial

Authors

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VERSION 1 - REVIEW

Reviewer	1
Name	Jiang, Li-ming
Affiliation	Shanghai University of Traditional Chinese Medicine, Shanghai Seventh People's Hospital
Date	12-Dec-2024
COI	None

Overview :

This study adopted a randomized double-blind sham-controlled design, preliminarily elucidating the feasibility, safety and analgesic effect of rTMS combined with exercise in the treatment of knee osteoarthritis, which has certain innovation and clinical significance. However, there are still some mistakes that need to be corrected. Specific comments can be found below.

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Overview

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Abstract

1. Line 35-36: It is shown here that 6 cases lost the follow-up at 3 months, while Figure 1 shows that 3 cases lost the follow-up. Please confirm if there is any discrepancy.

Introduction

2. The introduction mainly focuses on the background of the efficacy of rTMS combined with exercise on knee osteoarthritis (including central and peripheral mechanisms), but does not describe why the feasibility and safety of this program need to be studied. Please provide additional evidence on the possible risks of this program.

Safety

3. Line 15: There was a case of acute pain attributed to exercise. Please explain the basis

Discussion

4. Page 22, Line 24-25: 'AR+EX 81% vs SR+EX 75%', please confirm it.

Figures

5. Figure 3: Is there a difference in baseline levels in the modified painDETECT Questionnaire? Please confirm it.

Reviewer	2
Name	Yeh, Huan-Jui
Affiliation	Taoyuan General Hospital, PM&R
Date	04-Feb-2025
COI	None

This is a well-designed study with complete descriptive writing. The authors of this article describe the safety and patient acceptance of r-TMS combined with exercise therapy/ strength training for patients with OA knee, and analyze its therapeutic effectiveness.

major issue

The bigger problem is the novelty of the article. Because the safety of r-TMS has been recognized for several years, although only a small number of people have used it in OA knee before, there are actually a lot of literature on its use in pain control. When the intensity or frequency of treatment does not differ significantly from previous practices, it is less likely to interest readers to study patient acceptance or safety. For example, we already know that the drug for gastric ulcer is safe for most population of patients, so there is no need to study whether it is risky to use it on myopic patients, unless there is other theory or reason. The mechanism is used to illustrate the necessity of this research.

As the author wrote in the introduction, the current study gap lies in the lack of understanding of its treatment mechanism, and the lack of conclusion on whether it is effective or the strength of the effect. Therefore, the author can choose to arrange a future study of increasing the number of cases. OR, directly indicates that the results of this study show that r-TMS actually has limited efficacy and its ineffectiveness should be accepted. Also, the authors can do subgroup analysis about how to find truly effective treatment methods based on different treatment intensities, frequencies, or patient selections. Such articles may make better contributions in this field.

minor issue

1.Exclusion criteria 4th: why should patients who use steroids be excluded? What about patients who use other anti-inflammatory drugs or other analgesics? In addition, for point 11, please specify which similar drugs they are.

2. Exclusion criteria point 8: Very vague definition

3. no limitation part

VERSION 1 - AUTHOR RESPONSE

Response to reviewers' comments

Reviewer 1

Abstract

1. Line 35-36: It is shown here that 6 cases lost the follow-up at 3 months, while Figure 1 shows that 3 cases lost the follow-up. Please confirm if there is any discrepancy.

We thank the reviewer's comments. We have amended the text (page 3, line 35-36) which now reads:

"Eighty-six people were screened, 31 (36%) were randomised, 28 (90%) completed the treatments and three (10%) dropouts at three-month follow-up."

Introduction

2. The introduction mainly focuses on the background of the efficacy of rTMS combined with exercise on knee osteoarthritis (including central and peripheral mechanisms), but does not describe why the feasibility and safety of this program need to be studied. Please provide additional evidence on the possible risks of this program.

We have provided the rationale for the need to assess the feasibility and safety of this intervention in the Introduction. The text (page 7, paragraph 2, line 10) reads:

“A rigorous and adequately powered randomised controlled trial (RCT) is needed to determine the efficacy of this combined intervention of rTMS and strengthening exercise for knee osteoarthritis. Before conducting a full-scale RCT, a pilot study is recommended to inform the feasibility of the processes essential to the success of a large RCT and the safety of the intervention.(18)”

Safety

3. Line 15: There was a case of acute pain attributed to exercise. Please explain the Basis.

This participant in the sham rTMS + Ex group informed the chief investigator that knee pain was flared up the day after the first treatment. As it is unlikely that sham rTMS exerted effects to increase localised knee pain, it is reasonable to attribute the cause of this acute pain episode to the exercise component of the treatment. We have provided the explanation in the text (page 18, paragraph 1, line 4):

“One participant in the ST+EX group experienced an acute flare-up of knee pain after the first treatment and subsequently withdrew from the study. This acute episode of knee pain was attributed to strengthening exercise as it is unlikely that sham rTMS would yield negative effects on pain.”

Discussion

4. Page 22, Line 24-25: ‘AR+EX 81% vs SR+EX 75%’, please confirm it.

The success of participant blinding was presented in the Results section as following: “Thirteen participants (81%) in the AR+EX group and three (25%) in the SR+EX group correctly guessed their treatment group.” This indicates that 75% in the SR + EX group thought that they received active rTMS. Therefore, this statement in Discussion: “The proportion of participants thought they received active rTMS in both groups (AR+EX 81% vs SR+EX 75%) was similar” is correct.

Figures

5. Figure 3: Is there a difference in baseline levels in the modified painDETECT Questionnaire? Please confirm it.

As a pilot study has low statistical power, we did not include between-group comparisons in the planned analysis. Through visual inspection of Figure 3, it appears that modified painDETECT Questionnaire score at the baseline was higher in the AR + EX group than the SR + EX group. We have added this observation to the Discussion section. The text (page 23, paragraph 2, line 9) reads:

“Notably, baseline mPD-Q score in the AR + EX group was higher than the SR + EX group (see Figure 3). Based on the cut-off points for mPD-Q,(29) the AR + EX group displayed a possible neuropathic pain profile (13-18) whereas the SR + EX group displayed a nociceptive pain profile (≤ 12). While a recent clinical trial has demonstrated the efficacy of rTMS in chronic neuropathic pain,(24) whether this combined intervention is more efficacious in people with a neuropathic component of osteoarthritic knee pain cannot be inferred in this pilot study.”

Reviewer 2

Major issue

The bigger problem is the novelty of the article. Because the safety of r-TMS has been recognized for several years, although only a small number of people have used it in OA knee before, there are actually a lot of literature on its use in pain control. When the intensity or frequency of treatment does not differ significantly from previous practices, it is less likely to interest readers to study patient acceptance or safety. For example, we already know that the drug for gastric ulcer is safe for most population of patients, so there is no need to study whether it is risky to use it on myopic patients, unless there is other theory or reason. The mechanism is used to illustrate the necessity of this research. As the author wrote in the introduction, the current study gap lies in the lack of understanding of its treatment mechanism, and the lack of conclusion on whether it is effective or the strength of the effect. Therefore, the author can choose to arrange a future study of increasing the number of cases. OR, directly indicates that the results of this study show that r-TMS actually has limited efficacy and its ineffectiveness should be accepted. Also, the authors can do subgroup analysis about how to find truly effective treatment methods based on different treatment intensities, frequencies, or patient selections. Such articles may make better contributions in this field.

We thank the reviewer for the comments. While rTMS has been used in other chronic pain conditions with supporting evidence of its safety, this is the first clinical trial that combined rTMS with quadriceps strengthening for knee osteoarthritis. As stated in the text, this pilot study aimed to examine the feasibility and patient-perceived effect of this treatment, along with the safety. Before embarking a full-scale randomised controlled trial with adequate power to evaluate the clinical efficacy of this combined treatment, it is recommended conducted a pilot study to assess the feasibility of a large clinical trial.(1) This rationale has been added to the Introduction section (please see our response to Reviewer 1's comment). Due to the nature of a pilot study, we contend that the current study is not powered to conclude the efficacy of this combined treatment of rTMS and quadriceps strengthening exercise.(2) Future fully powered studies are needed to provide definitive evidence for the treatment efficacy and will also allow a robust investigation of the underlying mechanisms of this treatment and subgroup analysis to identify individuals who are more likely to respond to treatment. Our findings suggest a full-scale study is feasible and this combined treatment is safe, providing the supporting evidence for embarking future large RCTs.

Minor issue

1.Exclusion criteria 4th: why should patients who use steroids be excluded? What about patients who use other anti-inflammatory drugs or other analgesics? In addition, for point 11, please specify which similar drugs they are.

The 4th exclusion criterion is consistent with previous clinical trials investigating the effects of exercises for knee osteoarthritis,(3, 4) that people were excluded if they used oral corticosteroids currently or in the past 4 weeks. This is to ensure the effects of the study intervention on self-reported pain and function were not confounded by the potent anti-inflammatory effects of oral corticosteroids and catabolic effects on muscles (i.e., corticosteroid-induced myopathy).(5)

We did not exclude people who used other anti-inflammatory drugs or analgesics. This has been stated in the text (page 9, paragraph 1, line 5): "Participants were permitted to continue their usual medications during the trial."

We have added examples about neuroactive drugs and the text (page 8, the last line) reads:

“(11) use of neuroactive drugs (e.g., tricyclic antidepressant, Clozapine, Foscarnet);”

2. Exclusion criteria point 8: Very vague definition

To ensure any observed effects on pain and functional outcomes were the direct result of the study interventions, we excluded people who have been participating in strengthening exercise specific to knee osteoarthritis within six months before being screened for eligibility.

3. no limitation part

We have added study limitations in the Discussion section. The text (page 24, last line) reads:

“This study has some limitations. First, this pilot RCT was not powered to determine clinical efficacy, effects of the combined intervention of rTMS and strengthening exercise on pain and function in knee osteoarthritis cannot be inferred. Second, while self-reported WOMAC (physical function subscale) was used to assess function, objective outcome measures of physical function were not included in this study. The 2013 OARSI consensus recommends a set of performance-based tests for physical function in people with knee osteoarthritis.(50) According to this consensus, a minimal core set of three tests (i.e., 30-s chair-stand test, 40 m fast-paced walk test and stair-climb test) should be included as outcome measures to complement patient-reported measures in future large clinical trials.”

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