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Efficacy of Repetitive Transcranial Magnetic Stimulation on Improving Pain Severity in Patients with Chronic Knee Osteoarthritis

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Abstract:
Purpose: Knee osteoarthritis (KOA) is highly prevalent and leads to marked pain and dysfunction. Abnormal central changes were associated with KOA and its symptoms. Repetitive transcranial magnetic stimulation (rTMS) may improve these changes. This study aimed to evaluate the effect of (rTMS) on pain severity in patients with chronic knee OA.
Methods: thirty female patients with chronic knee osteoarthritis with age ranged from 40-65 years, were enrolled from neurophysiology department, Kars Al-Ainy hospital randomly and equally assigned into two groups (A and B); group A (experimental group, n=15) received (rTMS) plus conventional treatment (active mobilization, strength building and stretching exercises), while group B (control, n=15) received conventional treatment only. Treatment was daily session for five consecutive days, followed by one session per week for four weeks. Patients were assessed for pain using visual analogue scale (VAS) and pain detect questionnaire (PDQ).
Results: There were statistically significant improvement in PDQ scores, post-treatment in both groups and VAS significantly improved in group B only (p-value<0.05). In addition, there were no-significant differences post-treatment between groups (p-value>0.05). However, higher clinical improvements were detected in group A.
Conclusion: Exercises with/out rTMS improved pain in patients with chronic knee OA. However, addition of rTMS induced higher clinical improvements.
Key words: Exercises**,** Knee osteoarthritis, Knee pain, Repetitive transcranial magnetic stimulation.

1.Introduction

Chronic knee Osteoarthritis (KOA) is degeneration of the knee joint that affects all of its structures, progress overtime, and lasts ≥ four months. The prevalence and incidence of KOA are 23% and 654/1000 person-year in persons aged ≥ 40 years and increase with ageing. KOA causes significant pain, health and financial burden (1-4).

Chronic pain from KOA causes cranial plastic alterations (e.g. impaired GABAergic and glutamatergic activities) with reduced intracortical inhibition and increased corticospinal excitability causing central sensitization with decreased pain threshold and allodynia (5,6). Moreover, pain spreads past the joint and attains neuropathic characters (7).

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At a consequence, pain does not positively respond to traditional and more local interventions (weight loss, physical therapy modalities, medications, and surgery) (8,9). So, other therapies are needed. Of these, (rTMS) is suggested as it can stimulate the neural circuits that control pain and hence it is promising in management of chronic pain with central sensitization (10).

Studies that addressed the effect of rTMS on chronic knee pain from KOA are lacking (11). As well, the identified studies were limited by being case study, including healthy subjects, inducing pain experimentally, or being not applied repetitively (9,12-15).

So, the purpose of this study was to investigate the effect of rTMS on pain severity in patients with chronic knee OA.

2.Patients and Methods:

2.1. Study participants and recruitment criteria:

This study included a total of 30 patients with chronic KOA attending at neurophysiology department, Kasr Al-Ainy hospital, Cairo, Egypt. This study was conducted between December 2021 and May 2023.

Patients aged 40 to 65 years, referred by orthopedic surgeons with unilateral radiographic KOA (grade II and III on Kellgren-Lawrence classification), neuropathic pain (assessed by pain detect questionnaire), and pain for >3 months were included. Patients with rheumatoid arthritis, osteoporosis, fibromyalgia, neurological diseases, opioid or corticosteroid injection in the last month, history of knee surgery in the last six months, metallic implant on the face or skull, and history of convulsion were excluded.

2.2. Study Design:

This was a pretest posttest randomized controlled trial. The included patients were randomly and equally assigned into two groups (A and B); group A (experimental group) consisted of 15 patients who received rTMS plus a conventional exercises (active mobilization, strength building and stretching exercises), and group B (Control) consisted of 15 patients who received conventional exercises only. The study was ethically approved by research ethics committee of faculty of physical therapy, Cairo University (No: P.T.REC/012/004601). Written informed of all the participants was obtained.

2.3. Methods:

Interventions:

rTMS: patients were in sitting position. The rTMS of M1was performed using Magstim device which contains a coil coupled to a magnetic stimulator. The coil was put on M1 contralateral to the affected knee for 20 minutes**.** The parameters were 20 trains (7 seconds each) of 70 pulses, 10 Hz (inter-train duration: 55 s), and intensity of 80% of the resting motor threshold (16). One session daily for five consecutive days and followed by one session weekly for four weeks was applied**. (Figure 1**).

Fig. (1): rTMS

*Conventional exercises***:** It started with warming-up in form of five minutes walking. Then patients did active knee flexion and extension range of motion (2 sets of 10 repetitions with 3 seconds hold) from supine position with the affected leg. Then, they did strengthening exercises (2 sets of 10 repetitions with 6 seconds hold) in form of; isometric quadriceps exercises with knee extended from supine position by pressing against a pillow, leg press (against the wall from supine position with knees and hips at right angle), and semi squats with partial weight bearing (patients were standing with back against wall and did half squat up to 90-degree knee flexion with knees properly aligned), front step-up/down of a 10-cm step. Finally, they did stretching exercises (3 repetitions with 30 seconds hold) for; calf (patients positioned in standing in front of a wall and placed both hands on the wall and put the limb to be stretched backward with extended knee and heel on the ground and leaned forward), hamstrings (patients were in supine position, kept the untreated leg in extension and flexed the affected limb, keeping knee extended and ankle dorsi-flexed, with help of band), quadriceps (patients were in prone position, placed a band around the ankle to be stretched and held band with both hands and flexed the knee), and iliopsoas (patients stood up and put contralateral foot on a chair and leaned forward) (17-19).

2.4. Outcome measures:

Outcome measures were pain using visual analogue scale (VAS) and neuropathic pain using pain detect questionnaire (PDQ).

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Primary Outcome Measure:
Visual analogue scale (VAS): Knee pain was assessed by Visual analogue scale (VAS) (20).
Secondary Outcome Measure:
Pain *DETECT* questionnaire (PDQ): neuropathic pain was screened with Arabic version of pain *DETECT* questionnaire (PDQ) with score between 38 and –1. Patient was considered to have neuropathic pain if had score ≥15-19. It is valid and reliable in diagnosing chronic neuropathic pain (21).

3.DATA ANALYSIS:

Calculation of sample size:

Sample size calculation was based on power analysis done calculating the change in pain level with knee OA, the primary outcome of a previous study (22), using G*power software. Power set to (0.8) and significance level to (0.05). The calculation yielded a sample size of 38 participants in the two groups (n=19 in each group). However, only 30 patients could be included during the long period of this study as patients either did not have neuropathic pain or had significant fear from putting the device of their heads.

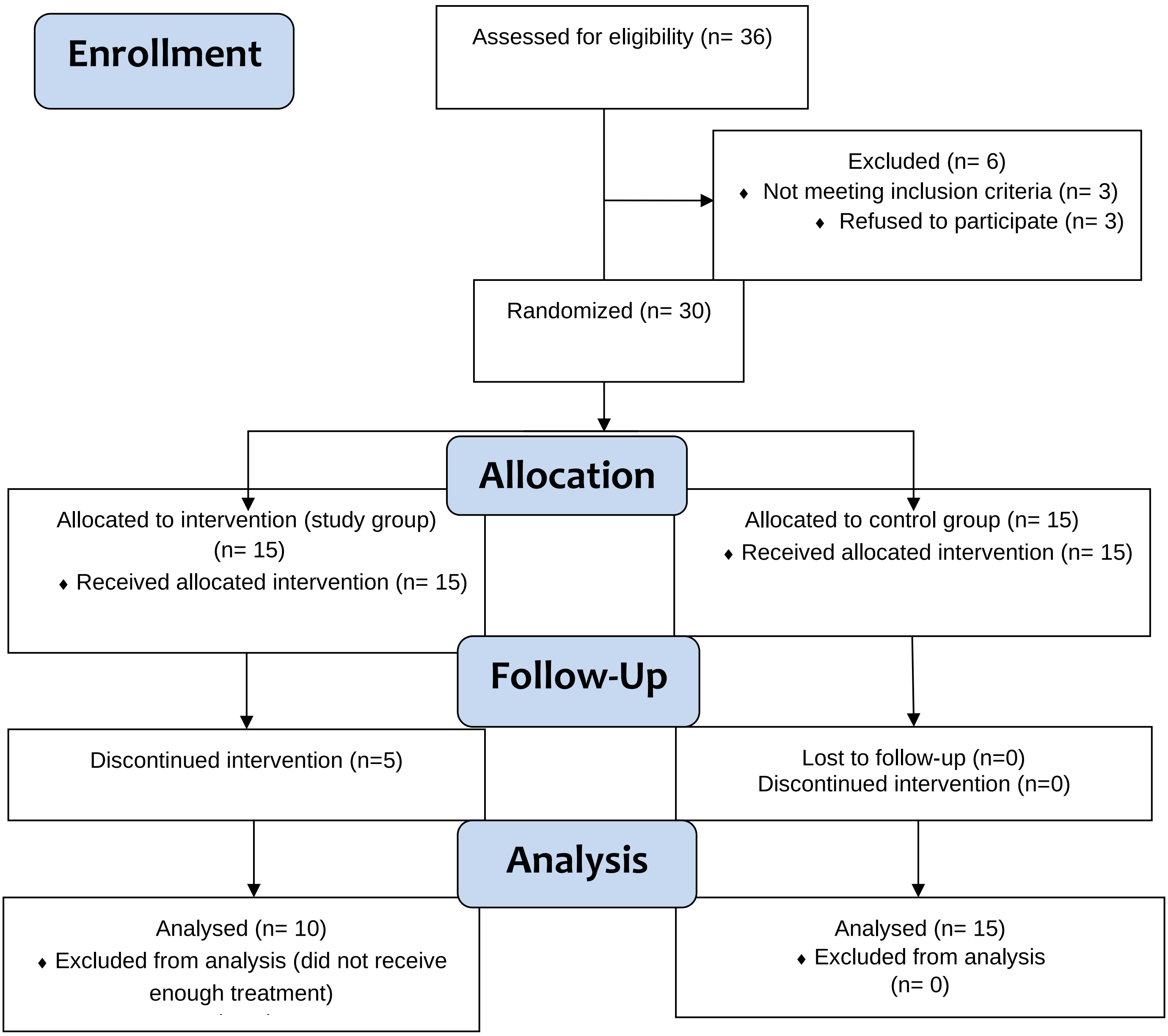

Figure (2): Study flow chart.

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Statistical Analysis:

Normality tests of data reflect that the data not significantly violates the assumption of normality except illness duration. No significant correlations were detected between dependent variables. Data were presented as means and SD except illness duration expressed as median and interquartile range. The differences between groups in all dependent variables and demographics (continuous) were done using independent t-test except illness duration analyzed with Mann-Whitney U test and sex distribution and affected side were tested with Chi-square test. Differences within groups were tested with paired t-test. All analyses were done using SPSS version 24 with the p-value set at ≤ 0.05.

4. Results:

(Table 1), statistically there was Nonsignificant difference between both groups related to age, and BMI and other baseline variables (P>0.05). Table 2 shows the mean (± SD) values of VAS and PDQ scores at pretreatment and post-treatment for both groups. There were significant improvements in PDQ post-treatment in both groups (p-value<0.05) and VAS scores in group A only. There were non-significant differences between groups at pre- and at post-treatment (P-value>0.05).

Table (1): Demographic data of patients in both groups

Qualitative variables	**Group A**	**Group B**	**P-value**
	Mean ± SD	**Mean ± SD**	
Age (years)	52.3±6.1	56.9±7.3	0.11
Weight (kg)	87.7±15.9	80.3±16.4	0.28
Height (cm)	165.2±1.6	166.6±2.6	0.14
BMI (kg/m2)	32.16±5.98	28.94±5.8	0.19
Gender (female%)	100	100	1
Duration of illness (months)^	12 (114)	84 (84)	0.2
Affected side (count, Right/Left)	5/5	5/10	0.41

SD: Standard deviation, BMI: body mass index, (^): Median (Interquartile range).

5. Discussion

This study aimed to evaluate the effect of repetitive transcranial magnetic stimulation on pain severity in patients with chronic knee OA.

The result of study showed that their significant improvement in PDQ scores post-treatment in both groups with higher clinical improvement in group A. While VAS significantly improved in group B only. However, there were non-significant differences post-treatment between groups.

Although, there was no significant improvement within group (A) in VAS, there were significant clinical improvements that exceed the minimal clinical important change. So, lack of statistical significance is due to small sample size.

Patients with KOA, severe pain, and chronic neuropathic pain had reduced regulation of pain signals that leads to pain persistence and fear behavior and cortical inhibition that occurs more in young patients with severe radiographic and mild symptomatic arthritis and leads to motor deficits (23-26).

Rehabilitation particularly exercise is the first line of treatment for people with OA for its beneficial effects (27). It increased resting state functional connectivity (rsFC) of the dorsolateral prefrontal cortex (DLPFC) to anterior cingulate cortex, thus decreased pain (19,28). This may explain the non-significant differences between both groups in the pain scores.

Findings of the current study regarding higher clinical improvement in VAS scores within rTMS group supports the notion that rTMS decreases pain by increasing pain threshold and endogenous opioids and activates deep brain areas (e.g. cingulate and PAG) responsible for pain modulation (descending inhibition) (11,29,30)**.**

As well, rTMS can decrease pain through changing intracortical inhibition or improving GABA function[31]. In addition to that, rTMS can improve synaptic efficiency and M1 excitability and kinesthetic sensitivity of muscle spindles (32,33). This may be the mechanism behind improved pain in rTMS group.

Moreover, this study supports that rTMS can treat patients with chronic pain and neuropathic pain with up to 50% pain reduction and hence improved life quality (6,11-13,29,31,32,34). In contrast to that, the current study found higher pain reduction that exceeded

87%. This may be due to longer duration of treatment with more sessions applied in the current study.

In concordance with the current study, Chipchase et al. (35), Petersen et al. (36), and Cardenas-Rojas et al. (37) found that the TMS positively influence pain and function in knee OA and chronic pain via counteracting maladaptive plasticity and improving pain modulation**.** The amount of improvement or the effect sizes were comparable between the present and previous studies (moderate to large effect sizes).

This study came in agreement with Nguyen et al. (8) who reported that rTMS (10 monthly sessions, 10 Hz, over the right motor cortex) reduced chronic pain (of central sensitization feature) related to knee OA by 67-70%. The present study found higher improvement (> 87%).

In agreement with Picarelli et al. (38) and Galhardoni et al. (13), there were some side effects reported by the patients during this study in form of fatigue and severe headache. However, they complications are different from that reported in previous studies being less severe or less risky but caused patients to drop out from the study.

This study came in line with the recent review by Sorkpor and Ahn (39) about effect of rTMS on chronic pain conditions that revealed beneficial effects for rTMS.

The rTMS, being tolerated by the patients with few side effects and being effective in improving pain, should be combined with the conventional program for the treatment of chronic osteoarthritic pain with neuropathic features (14).

This study is limited by including small sample size (due to drop-outs and fear from participation) that was totally from female gender limiting the generalizability or external validity of the study. It also did not include true control group.

Conclusion:

According to previous discussions of these results and reviews of academic research associated with the current study, it is possible to state that exercises with/out rTMS improved pain in patients with chronic knee OA. However, addition of rTMS induced higher clinical improvements.

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