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# Efficacy of Manual Therapy on Facilitatory Nociception and Endogenous Pain Modulation in Older Adults with Knee Osteoarthritis: A Case Series

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**Abstract:** Background: manual therapy (MT) has been shown to have positive effects in patients with osteoarthritis (OA)-related pain, and its use in clinical settings is recommended. However, the mechanisms of action for how these positive effects occur are not yet well understood. The aim of the present study was to investigate the influence of MT treatment on facilitatory nociception and endogenous pain modulation in patients with knee OA related pain. Methods: Twenty-eight patients with knee OA were included in this study. Pain intensity using the numerical pain rating scale (NPRS), temporal summation (TS), conditioned pain modulation (CPM), and local (knee) and distant (elbow) hyperalgesia through the pressure pain threshold (PPT), were assessed to evaluate the pain modulatory system. Patients underwent four sessions of MT treatments within 3 weeks and were evaluated at the baseline, after the first session and after the fourth session. Results: the MT treatment reduced knee pain after the first session ( $p = 0.03$ ) and after the fourth session ( $p = 0.04$ ). TS decreased significantly after the fourth session of MT ( $p = 0.02$ ), while a significant increase in the CPM assessment was detected after the fourth session ( $p = 0.05$ ). No significant changes in the PPT over the knee and elbow were found in the follow-ups. Conclusions: The results from our study suggest that MT might be an effective and safe method for improving pain and for decreasing temporal summation.

**Keywords:** knee osteoarthritis; manual therapy; diffuse noxious inhibitory control; conditioned pain modulation; temporal summation; central sensitization

## 1. Introduction

Osteoarthritis (OA) is considered a progressive chronic degenerative disease of the articular cartilage in the synovial joints [1] and is one of the most common types of rheumatic disease [2], affecting 303 million people worldwide [3].

The diagnosis of knee OA is mainly based on the identification of its symptoms and is confirmed by an imaging diagnosis according to the criteria of the American College of Rheumatology (ACR) and the Kellgren and Lawrence scale [4]. However, pain phenotypes in OA patients vary considerably, and often do not correlate with the severity of radiographic findings [5]. Emerging evidence suggests that alterations in pain processing within the peripheral and/or central nervous system (CNS) may be a crucial factor in accounting for the various clinical presentations of pain related to OA [6].

Neurophysiologically, central sensitization (CS) is characterized by an increase in the afferent nociceptive information that could increase the excitability of neurons in the spinal dorsal horn [7]. This phenomenon would facilitate a possible sensitization at a central level, leading to signal amplification within the CNS, hypersensitivity to pain, and referred pain [8,9]. Spinal cord neurons also receive information from other tissues that are far from the painful area of joint damage, such as the muscle or peri-articular tendon, generating a dysfunction of the downstream inhibitory mechanisms and an increase in temporal summation (TS) and conditioned pain modulation (CPM) alterations [10,11]. Therefore, one of the main objectives of any treatment is to improve the pain modulation systems.

Psychosocial factors (cognitive factors, emotional factors, behavioral factors, social factors) also play a key factor in sensitizing the CNS [7]. The biopsychosocial approach in understanding the interaction between psychological and physical factors is a topic of primary importance, especially for its association with chronic pain [12]. Reducing the impact of stress and psychological factors could have a positive impact on the experience of pain, making the assessment of social, behavioral, and contextual factors necessary in pain trials.

Manual therapy (MT) can be considered an effective treatment in the management of pain in knee OA, decreasing the pain threshold and cortical excitability. Indeed, systematic reviews support a transient pain inhibitory effect of manual therapy on psychophysical measures [13,14]. Previous studies have investigated the reduction of pain associated with the normalization of TS and CPM variables in patients with knee OA [15,16]. Pain mechanistic-based treatment strategies for MT give us an interesting approach for identifying patients likely to respond to MT [17]. Despite this, there is a current lack of knowledge regarding the pain mechanisms through which MT treatment induces a positive effect on musculoskeletal patients.

The mobilization with movement technique (MwM) is a joint mobilization method based on the concurrent application of sustained mobilization applied by a therapist and an active physiological movement performed by the patient. MwM has been shown to generate hypoalgesia by stimulating the spinal dorsal horn with non-painful information. On the other hand, articular accessory mobilizations try to achieve similar effects by increasing the range of movement, reducing pain and restoring optimal kinematics between articular surfaces [18]. However, the effects of MT treatment on pain processing and endogenous pain modulation remain under investigation.

Therefore, the main objective of this study was to investigate the influence of the MT treatment on facilitatory nociception and endogenous pain modulation in older adults with knee OA.

## 2. Materials and Methods

### 2.1. Study Design

A case series of 28 consecutive patients with knee OA (Kellgren and Lawrence scale between 1–3) was recruited from the physiotherapy departments of “Manuel Herranz Esclavas de la Virgen Dolorosa” older-adult care center in Pozuelo de Alarcón, Madrid and “Parque Coimbra” older-adult care center in Móstoles, Madrid between January and

March 2020. It was approved by the Clinical Research Ethics Committee of the Rey Juan Carlos University, Madrid, Spain (approval number: 0902201803618).

## 2.2. Participants

Twenty-eight consecutive patients over 65 years old meeting the American College of Rheumatology (ACR) clinical criteria for a knee OA diagnosis [19] with low or null response to analgesic medication were recruited. A non-probabilistic method of judgmental or purposive sampling was performed. A Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [20] and a timed up and go (TUG) [21] test were performed at the first evaluation to investigate the patients' functionality at baseline conditions. Psychological measures such as depression (Beck Depression Inventory [22]), anxiety (State-Trait Anxiety Inventory [23]), and kinesiophobia (Tampa Scale of Kinesiophobia [24]), and cognitive measures such as catastrophizing (pain catastrophizing scale) were also assessed at the baseline (Table 1).

**Table 1.** Characteristics of the participants at baseline.

Characteristics	Group ( <i>n</i> = 28)
Age (y), mean (SD)	87 ± 8
Gender, <i>n</i> female (%)	20, (71.4%)
NPRS	5.72 ± 2.9
Temporal Summation	2.6 ± 2.1
Conditioned Pain Modulation	3.1 ± 1.1
PPT-knee, (kg/cm <sup>2</sup> )	3.2 ± 1.2
PPT-elbow, (kg/cm <sup>2</sup> )	3.4 ± 1.4
Beck Depression Inventory II	9.8 ± 7.2
Tampa Scale of Kinesiophobia	24.8 ± 12.5
STAI	18.2 ± 13.1
WOMAC	38.7 ± 19.0
Time Up and Go Test	23.7 ± 18.3
Pain Catastrophizing Scale	9.4 ± 11.1

SD: standard derivation; NPRS: numeric pain rating scale; PPT: pressure pain threshold; STAI: state-trait anxiety inventory; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Exclusion criteria for all subjects were the following: patients with a body mass index (BMI)  $\geq 25$ ; presence of any syndrome or disease compatible with myofascial or neuropathic pain in lower limbs; corticoid or local anesthetic injection in the previous year or during the treatment; previous lumbopelvic or lower limb surgery; contraindications to receive MT; and previous diagnosis of myopathy, neuropathy or cognitive impairment. Informed consent was obtained from all the subjects and the study followed the principles outlined in the Declaration of Helsinki.

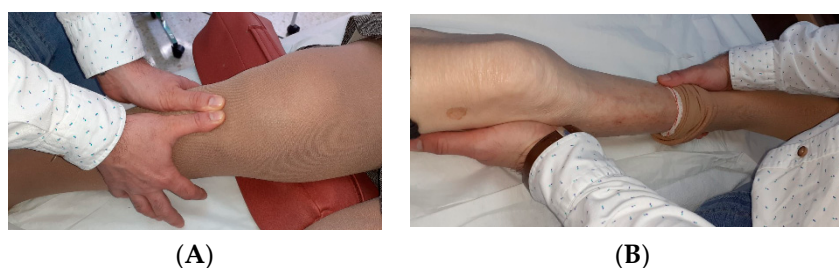
## 2.3. Intervention

Twenty-eight participants underwent either the articular accessory mobilizations or the mobilization with movement treatment the day after being assessed. They underwent the other 3 sessions of the treatment in the following 3 weeks, receiving 4 total sessions of treatment.

The articular accessory joint mobilization technique was executed with the patient in supine position with a pillow under their knee, granting them slight knee flexion in order to facilitate gliding. Then, physiological (flexion and extension) and accessory (anteroposterior, posteroanterior) movements were evaluated for pain and/or restriction [25].

The technique was executed by placing both hands on the knee of the subject and gliding the tibia forward and back (posteroanterior) or vice versa (anteroposterior), based on the patient's pain relief, on the femur in an oscillatory manner (Figure 1A). The range of motion of the technique was based on the patient's severity and irritability instead of the classic Maitland grades of movement, as other studies have demonstrated that a large amplitude and small amplitude of mobilization did not produce statistically significant

differences in terms of pain relief [26]. Each treatment was applied for 2 sets of 3 min with 30 s of rest interval between [16].



**Figure 1.** (A,B) In these two images we can see the positions and the manual forces developed in each technique: (A) articular accessory joint mobilization technique; (B) mobilization with movement technique.

In the mobilization with movement technique, with the patient in supine position, the range and direction of the painful knee movement (flexion or extension) performed by the subject were identified. Each patient was tested with different sustained glides in each position (medial glide, lateral glide, medial rotation and lateral rotation of the tibia on femur), looking for the glide that resulted in the painful movement becoming pain-free and improving the range of motion (considering the baseline NRPS value) [27]. These gliding techniques were described by Mulligan in his textbook (Mulligan BR 2004 Manual Therapy: “NAGS”, “SNAGS”, “MWMS” Etc. Wellington, New Zealand, Plane View Services) (Figure 1B). If two or more glide directions produced the same effects in a supine position, a weight-bearing position was tested to determine the best glide [27].

If the movement combined with the glide showed no change in pain or increased the pain beyond 3 repetitions, the glide had to be changed. For whichever glide made the movement pain-free when applied to the painful movement beyond 3 repetitions, the repetitions were continued further as per the response of the reduction in pain to the mobilization. Each treatment was applied for 3 sets of 10 repetitions, as other studies did [27].

#### 2.4. Outcomes Measurement

The primary outcome measures were the intensity of pain as assessed by the numerical pain rating scale (NPRS), TS, CPM, and pressure pain threshold (PPT). These measures were assessed at the baseline, the day after the first session and the day after the last session (fourth session). The same physiotherapist carried out the pain, function, and test assessments.

##### 2.4.1. Numeric Pain Rating Scale

Pain intensity was measured with the NPRS of 11 points (interval from 0 to 10), where 0 corresponds to no pain and 10 corresponds to the worst pain imaginable. The patients were asked to assess the subjective pain intensity of the painful knee at rest, in maximum flexion, in maximum extension, in the best moment of the day, and in the worst moment of the day. The NPRS is a valid and reliable tool in the assessment of older adults, and its correlation with the VAS shows a high convergent validity (0.79–0.95) [28].

##### 2.4.2. Pressure Pain Threshold

A handheld pressure algometer (Model FDIX, Wagner Instrument Mark, Greenwich, CT 06836-1217, USA) with a 1 cm diameter flat rubber probe was used to evaluate the PPT. The PPT was assessed at two points marked at the painful knee joint interline and at the lateral epicondyle of the ipsilateral arm. Pressure was applied manually at approximately 0.5 kg/s on the test site [29] and the minimal amount of pressure that produced pain was detected. Three PPT measurements following the sequence knee–elbow were recorded from each test site with a minimum interval of 10 s [30,31]. The average threshold values (kg/cm<sup>2</sup>) have been considered for the analysis. The PPT near to the pathological site

was thought to represent the degree of peripheral nociception, whereas the PPT distant to the pathology is a valid indicator of CNS hyperexcitability [32]. The reproducibility and reliability of the results obtained by using algometry to measure the pressure pain threshold have been previously demonstrated [16,33].

#### 2.4.3. Temporal Summation

TS was evaluated using the previously described handheld pressure algometer. TS was elicited with 10 pressure stimulations at the pressure pain detection threshold intensity following a specific protocol subsequently described. Pressure stimulation was applied at 3 cm lateral to the patellar edge of the painful knee. TS elicitation commenced 2 min after the PPT was taken in order to avoid possible sensitization from pain threshold stimulation. For each pulse, the pressure was increased at a rate of approximately 2 kg/s up to the previously determined pain threshold [34]. Pulses were presented with an interstimulus interval of 1 s because this has previously been shown to be optimal for inducing TS with pressure pain [35]. Before the first pulse, subjects were instructed to orally rate the pain level of the first and tenth pulse with the NPRS. The TS value is the result of the subtraction of the NPRS value at the tenth pulse from the NPRS value at the first pulse.

#### 2.4.4. Conditioned Pain Modulation

The same pressure algometer with a 1 cm diameter flat rubber probe was used to evaluate PPT before and during the conditioning stimulus. Ischemic muscle pain was used as a conditioning stimulus using a sphygmomanometer (Model Minimus® II, Rudolf Riester, Germany). The sphygmomanometer was applied around the contralateral upper limb (lower rim 3 cm proximal to the cubital fossa). A first PPT was measured 3 cm lateral to the patellar edge of the painful knee before inflating the cuff (PPT without stimulus). Afterwards, the cuff was inflated to 260 mmHg and maintained until the subjects perceived a 6/10 pain on the NPRS, and PPT was detected during this conditioning stimulus at the same place on the knee [36]. The CPM value is the result of the subtraction of the value of the PPT during the conditioning stimulus minus the PPT without stimulus.

#### 2.4.5. Statistical Analysis

The data were analyzed using the SPSS package version 25.0 (SPSS Inc, Chicago, IL, USA). The normal distribution of the sample was analyzed by using the Kolmogorov–Smirnov test. A one-way analysis of variance (ANOVA) with repeated measurements and Bonferroni was used as a post-hoc test to evaluate statistical significance. Within-group effect sizes were calculated using the Cohen *d* coefficient [37]. An effect size greater than 0.8 was considered large, around 0.5 moderate, and less than 0.2 small. For all the data of the study, *p*-values lower than 0.05 were considered significant.

### 3. Results

The baseline characteristics of the 28 patients (mean age  $87.3 \pm 8.3$  years; 8 male and 20 female) are listed in Table 1. We found no differences in the demographic variables and in the baseline levels of the primary outcome (NPRS, TS, CPM and PPT). No subjects dropped out during the different phases of the study, and no adverse effects were detected after the application of the treatments. None of the subjects began drug therapy during the course of the study.

#### 3.1. Knee Pain Intensity

At baseline assessment, the patients presented an intensity of pain in the knee of  $5.7 \pm 2.9$  ( $F = 4.153$ ,  $p = 0.021$ ). In contrast, NPRS after the first session treatment decreased to  $4.2 \pm 3.03$ , ( $p = 0.03$  vs. Pre-treatment;  $n = 28$ ), and after the fourth session, patients presented an NPRS in the knee of  $4.0 \pm 2.6$ , ( $p = 0.04$  vs. Pre-treatment;  $n = 28$ ), Table 2. Within-group effect sizes were moderate in the post-treatment period ( $d < 0.8$ ).



**Table 2.** Mean (SD) and mean difference within the group for numeric pain rating scale, temporal summation, pain modulation and pressure pain threshold at all study visits.

	Baseline	1st Session	4th Session	Cohen's d
	Pain intensity, NPRS			
Knee	5.7 ± 2.9	4.2 ± 3.03 *	4.0 ± 2.6 *	0.6
	PPT (kg/cm <sup>2</sup> )			
Knee	3.2 ± 1.2	3.5 ± 1.4	3.7 ± 1.6	0.4
Elbow	3.4 ± 1.4	3.6 ± 1.3	4.1 ± 1.9	0.4
	Temporal Summation			
	2.6 ± 2.1	1.5 ± 1.5	0.6 ± 1.5 *	1.1
	Conditioned Pain Modulation			
	3.1 ± 1.1	3.3 ± 1.2	3.8 ± 1.4 *	0.6

NPRS: Numeric pain rating scale; PPT: pressure pain threshold; \* Indicates statistical significance  $p < 0.05$ .

### 3.2. Mechanical Pain Sensitivity

We found no significant differences for time in PPT over the knee and elbow, which had values of  $3.21 \pm 0.04$  kg/cm<sup>2</sup> ( $F = 2.871$ ,  $p = 0.07$ ) and  $3.42 \pm 1.4$  kg/cm<sup>2</sup> ( $F = 3.5$ ,  $p = 0.08$ ), respectively (Table 2). Within-group effect sizes were small in the post-treatment period ( $d < 0.5$ ).

### 3.3. Temporal Summation

At baseline assessment, the patients presented a TS value of  $2.64 \pm 2.1$  ( $F = 4.832$ ,  $p = 0.01$ ). In contrast, TS after the first session decreased to  $1.5 \pm 1.5$  ( $p = 0.06$  vs. pre-treatment;  $n = 28$ ), and after the fourth session of treatment, patients presented a TS value of  $0.61 \pm 1.5$ , ( $p = 0.02$  vs. pre-treatment;  $n = 28$ ) (Table 2). Within-group effect sizes were greater in the post-treatment period ( $d > 0.8$ ).

### 3.4. Conditioned Pain Modulation

Patients with knee OA before the treatment presented a CPM mean value in the knee of  $3.10 \pm 1.1$  ( $F = 4.893$ ,  $p = 0.01$ ). After the fourth session of MT, patients presented comparable levels at  $3.8 \pm 1.4$ , ( $p = 0.05$ ; vs. pre-treatment;  $n = 28$ ). The CPM remained at the same level after the first session (Table 2). Within-group effect sizes were moderate in the post-treatment period ( $d < 0.8$ ).

## 4. Discussion

The main results of the present study suggest that in patients with knee OA, MT implies a decrease in the neuronal excitability in the spinal cord by means of a reduction in the TS after the application of four treatment sessions. MT led to a significant knee pain reduction after the first session and after the fourth session, while significant changes in the CPM and in the TS assessment were detected after the fourth session.

Our study found significant changes in pain intensity after first and fourth session treatments. Rao et al. [25] in a recent study compared two manual therapy techniques showing improvement in the pain intensity parameter after the intervention; moreover, the improvements occurred in both groups without any differences between the techniques. In addition, Bhagat et al. [38] compared the effects of MwM mobilization with sham mobilization, finding a statistically significant decrease in the NPRS value post-treatment in both groups.

In the literature, few studies assess the changes in TS following the application of MT in patients with knee OA. In a recent study, Lluich et al. [34] performed four sessions in four weeks of MT combined with either biomedical education or pain neuroscience education, investigating the TS in patients with knee OA. They did not find any significant improvements on the TS parameters after four sessions of MT nor at one month of follow-

up in any of the considered groups. Instead, in our study, significant decreases in TS were found after the fourth session compared to the baseline measurement.

In the present study, no significant changes in the PPT were detected in the lateral epicondyle and locally at the level of the knee after the first and fourth MT session. This is in contrast with the study of Courtney et al. [39], which defined that MT could reverse hyperalgesia at a local and a distant site, therefore suggesting effects at a central level. Despite this, in a previous published study by Courtney et al. [16] the knee PPT significantly improved immediately after joint mobilization, suggesting that joint mobilization may aid in facilitating central inhibitory mechanisms. In contrast with our study, Alkhawajah et al. [27] found that MT resulted in greater immediate improvement of the PPT at the painful site and at a distant site (shoulder) in knee OA patients.

The effect on the pain modulatory system, especially relative to the TS, could be explained by the neurophysiological effects that MT has been shown to produce on the CNS [40]. The hypothesis that MT would improve the facilitatory nociception and endogenous pain modulation, causing a reduction in the maladaptive mechanisms observed in the pain neuromatrix in patients with knee OA, remains an issue of clinical interest [41–44]. However, after the results of this study and the discussion based on the results of similar studies, a question may arise as to the possible relationship between the MT applied and the level whereat the greatest effect would occur.

#### *Limitations*

The present study has a number of limitations that could influence the results obtained, so they will have to be taken into account in similar future studies. The major limitation is that the MT technique has not been compared with a placebo/sham group and no specific effects can be agreed. Another significant limitation is that only the short-term effects were measured, thus precluding conclusions regarding the long-term effects. Finally, we recognize that the sample size was small, although sufficient to determine significance.

#### **5. Conclusions**

The results from our case series suggest that MT might be effective and safe for improving the neuronal excitability in the spinal cord by means of a reduction of the TS after the application of four treatment sessions in patients with knee OA. However, our recommendations are weak due to the limitations of the study and the lack of a control group. Clinical use of MT is traditionally supported by the concept of a peripheral action; however, changes on the facilitatory nociception and endogenous pain modulation system were shown in the present study. High-quality RCTs with long-term follow-up are warranted to confirm our findings.

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**Data Availability Statement:** Data available on request due to privacy and ethical restrictions.

**Conflicts of Interest:** The authors certify that they have no affiliations with or financial involvement in any organization or entity with a direct financial interest in the subject matter or materials discussed in the article.

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