Preoperative Pain Neuroscience Education Combined With Knee Joint Mobilization for Knee Osteoarthritis

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Preoperative pain neuroscience education combined with knee joint mobilization for knee osteoarthritis: a randomized controlled trial

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ABSTRACT

Objectives: To compare the effects of a pre-operative treatment combining pain neuroscience education (PNE) with knee joint mobilization versus biomedical education with knee joint mobilization on central sensitization (CS) in subjects with knee osteoarthritis (KOA), both before and after surgery. Secondly, to compare the effects of both interventions on knee pain, disability and psychosocial variables.

Methods: Forty-four subjects with KOA were allocated to receive four sessions of either PNE combined with knee joint mobilization or biomedical education with knee joint mobilization before surgery. All participants completed self-administered questionnaires and quantitative sensory testing was performed at baseline, after treatment and at a one month follow-up (all before surgery) and at three months after surgery.

Results: Significant and clinically relevant differences before and after surgery were found after both treatments for knee pain and disability and some measures of CS (i.e. widespread hyperalgesia, central sensitization inventory), with no significant between-group differences. Other indicators of CS (i.e. conditioned pain modulation, temporal summation) did not change over time following either treatment and in some occasions the observed changes were not in the expected direction. Subjects receiving PNE with knee joint mobilization achieved greater improvements in psychosocial variables (pain catastrophizing, kinesiophobia) both before and after surgery.

Discussion: Pre-operative PNE combined with knee joint mobilization did not produce any additional benefits over time for knee pain and disability and CS measures compared with biomedical education with knee joint mobilization.

Superior effects in the PNE with knee joint mobilization group were only observed for psychosocial variables related to pain catastrophizing and kinesiophobia.

Key Words: Knee osteoarthritis, central sensitization syndromes, physical therapy, education

INTRODUCTION

The experience of pain in knee osteoarthritis (KOA) is a multifactorial phenomenon attributed to knee structural changes ocurring together with psychosocial and pain neurophysiology factors[1]. Regarding the latter, there is compelling evidence that central sensitization (CS) is a prominent phenomenon in a subgroup of people with KOA[2]. Despite the increased emphasis on the importance of CS in KOA[3], current KOA treatments don't usually specifically address altered nociceptive processing mechanisms[4]. Indeed most evidence-based recommendations for KOA management[5,6] don't consider pain mechanisms and its possible modulation by treatment.

Some studies have investigated the effects of treatments used for KOA on central pain modulation using outcome measures related to CS [e.g., the flexor withdrawal reflex[7] and conditioned pain modulation (CPM)[8]]. In those studies, CS was down-modulated after knee joint mobilization[7-9], exercise[10], TENS[11], surgery[12] or a combination of interventions[13]. Combined treatments consisting of locally-applied and centrally-oriented interventions have been proposed for KOA[14,15], aiming at synergistic effects and consequently an improvement of outcomes.

Within this view of combined treatments, the rationale for applying pain neuroscience education (PNE) together with knee joint mobilization was recently presented[14], but requires experimental testing. On one hand, knee joint mobilization may produce beneficial effects on pain and function in KOA[16,17] as well as modulating effects on CS[7-9]. On the other hand, PNE is a useful intervention for chronic pain populations characterized by CS, especially when administered with other physical therapy interventions[18]. Enhancement of CPM

was shown following PNE[19] and, when applied before surgery, PNE produced favorable post-surgical outcomes in people with lumbar radiculopathy[20]. As the pre-surgical presence of CS in KOA contributes to poor outcomes after total knee replacement[21], preoperative PNE combined with other interventions[18] might be beneficial.

The primary aim of this study was to compare the effects of a pre-operative treatment combining PNE with knee joint mobilization versus biomedical education with knee joint mobilization on measures of CS in people with KOA, both before and after surgery. Secondly, the effects of both interventions on knee pain, disability and psychosocial variables were investigated. We hypothesized that PNE with knee joint mobilization would result in significantly larger improvements in CS and psychosocial factors in patients with KOA, both before and after surgery.

MATERIALS AND METHODS

Study design

A two-arm, parallel group, assessor blinded, randomized controlled trial conforming to CONSORT guidelines[22] was performed between January 2014 and February 2015, at the Hospital Universitario La Ribera (Alzira, Spain). The study was approved by the Human Research Ethics Committee of the Hospital Universitario La Ribera and conducted in accordance with the Declaration of Helsinki. The study was registered at ClinicalTrials.gov (Trial Registration NCT02246088).

Participants

People with KOA pain of more than 3 months duration and scheduled to undergo total knee replacement were enrolled. They were recruited from the Orthopedic Surgery Service of the Hospital Universitario La Ribera, Spain.

Individuals were included if they had symptomatic KOA according to the American College of Rheumatology classification criteria[23]. All participants underwent weight bearing, fixed flexion posteroanterior and lateral X-rays of their affected knee. Radiographic disease severity of the tibiofemoral (Kellgren–Lawrence 0–4 grading scale[24]) and patellofemoral (Ahlbäck 0-5 grading scale[25]) compartments were evaluated for each participant.

Subjects were excluded if they had previous total knee replacement or any other lower limb surgery within the past six months of the affected knee, co-existing inflammatory, metabolic or neurological disease, chronic widespread pain (i.e., fibromyalgia), cognitive impairment, illiteracy, or were unable to speak or write Spanish.

Subjects were informed about the procedures and gave written informed consent prior to participation.

Procedure

Demographic information was first collected by self-report. Additionally, participants completed an 11-point numeric rating scale to quantify their current pain intensity overall during the last week.

They then completed the following self-administrated questionnaires: the Western Ontario and McMaster Universities Arthritis Index (WOMAC), Central Sensitization Inventory (CSI), Pain Catastrophizing Scale (PCS) and 11-item

version of the Tampa Scale for Kinesiophobia (TSK-11). Finally, all participants were assessed by quantitative sensory testing to examine pressure pain thresholds (PPTs), temporal summation and CPM in one single session. Participants were requested not to take analgesic medication 24h before the assessment.

A physical therapist, specifically trained in all aspects of the assessment, was responsible for all the measurements. This assessor was blinded to the questionnaire data and to the treatment allocation.

Outcome Measurements

The primary outcome measure was CPM which is a recognized objective biomarker of CS[3]. Secondary outcomes were PPTs, temporal summation and results from the questionnaires. Every outcome was measured at baseline (2 months before surgery), immediately after four treatment sessions (1 month before surgery), at one month follow-up (just before surgery) and three months after surgery.

Assessment of CS

Pressure pain thresholds

A standardized protocol for evaluating PPTs was used[26]. Two test sites in the peripatellar region (3 cm medial and lateral to the midpoint of the medial and lateral edge of patella, respectively) and one distant site on the ipsilateral extensor carpi radialis longus (5 cm distal to lateral epicondyle) were selected for measurement[27]. The PPT was measured using an analogue Fisher algometer (Force Dial model FDK 40) with a surface area of 1cm^2. The

algometer probe tip was applied perpendicular to the skin at a rate of 1kg/cm^2/s until the first onset of pain. Three measures were performed on each site with a 30 s interstimulus interval between each measurement and the mean was taken for analysis. For PPTs, a 1.62-1.53 kg/cm^2 is the minimum detectable change required to be clinically meaningful in people with KOA[28].

Temporal summation and Conditioned pain modulation

The protocol described by Cathcart and colleagues was used for measuring temporal summation and CPM[29], which are established ways of measuring excitability of nociceptive pathways and descending pain inhibition, respectively[30,31].

First, PPTs were measured at the local and distal sites as described above. Second, temporal summation was provoked by means of 10 consecutive pulses at the previously determined PPT at each location. For each pulse, pressure was gradually increased at a rate of 2 kg/s to the determined PPT and maintained for 1 s before being released (1 s interstimulus interval). Pain intensity of the 1st, 5th, and 10th pulse was rated on a numerical rating scale (0: no pain to 10: worst possible pain). Afterwards, a rest period of 5 min was given.

Third, CPM was induced by combining the temporal summation procedure (test stimulus) and an inflated occlusion cuff around the subject's arm, contralateral to the side of the affected knee, to a painful intensity (conditioning stimulus). The occlusion cuff was inflated at a rate of 20 mm Hg/s until 'the first sensation of pain' and maintained for 30 s. Pain intensity as a result of cuff inflation, was then rated on a numerical rating scale. Next, cuff

inflation was increased or decreased until the pain intensity was rated as 3/10. Temporal summation assessment was then repeated during maintenance of the cuff inflation[29].

The details and data supporting the test-retest reliability and validity of the protocol for examining temporal summation and CPM are described elsewhere[29].

Central Sensitization Inventory (CSI)

The CSI is a self-report screening instrument that helps to identify key symptoms associated with CS[32]. Part A of the CSI assesses increased responsiveness to a variety of stimuli and is comprised of 25 items each ranged on a 5-point scale with the end points “never” (0) and “always” (4) (range: 0-100). The CSI has high reliability and validity[32]. A cutoff score of 40 distinguished between individuals with central sensitivity syndromes and a non-patient comparison sample (sensitivity = 81%, specificity = 75%)[33]. The following CSI severity levels have been established for interpreting CSI scores: subclinical = 0 to 29; mild = 30 to 39; moderate = 40 to 49; severe = 50 to 59; and extreme = 60 to 100[34]. The Spanish version of the CSI was used in this study.

Knee pain and disability

The total WOMAC score (range 0-96) was considered with higher scores indicating worse knee pain and disability. Test-retest reliability, internal consistency, convergent validity and responsiveness of the Spanish version of

the WOMAC has been demonstrated in people with KOA[35]. A 7.9-point change is required for the result of WOMAC to be clinically meaningful[36].

Psychosocial variables

Pain catastrophizing

The Pain Catastrophizing Scale (PCS), which is a valid and reliable instrument to measure pain catastrophizing, was used[37]. It consists of 13 items each ranged on a 5-point scale with the end points (0) “not at all” and (4) “all the time” (range: 0-52). Higher scores indicate higher pain catastrophizing. The Spanish version of the PCS has appropriate internal consistency, test-retest reliability and sensitivity to change[38].

Kinesiophobia

The Spanish version of the TSK-11 was used to measure fear of movement[39]. It consists of 11 items each ranged on a 4-point scale with the end points (1) “totally agree” and (4) “totally disagree” (range: 11-44). The TSK-11 has demonstrated acceptable internal consistency and validity (convergent and predictive)[39]. Higher scores indicate more fear-avoidance behavior. The minimal detectable change score for the TSK-11 is 5.6[40].

Interventions

An equal number of participants were randomly allocated by the computer program EPIDAT version 3.1, to receive either PNE plus knee joint mobilization (experimental treatment) or biomedical education plus knee joint

mobilization (control treatment). The researcher administering the randomization schedule was different from those who recruited the participants.

In both groups, the educational part of the intervention preceded knee mobilization[14] and participants were blinded to the type of education they received. Both programmes involved a total of four treatment sessions (one session per week), commencing two months prior to surgery and finishing one month prior to surgery in all participants. Researchers sent repeated reminders to participants by email and made phone calls to ensure adherence to this time schedule. All interventions were applied by a physiotherapist experienced in providing educational and knee joint mobilization procedures. This therapist was blinded to the results of the measurements and questionnaires which were used as outcome measures.

All participants were instructed to continue to take any current medications but not to start new medications or initiate new treatments during the treatment period.

PNE with knee joint mobilization

PNE and knee joint mobilization were applied following previous published guidelines[14] by a physiotherapist trained extensively by expert therapists in the domain of PNE and knee joint mobilization techniques. The therapist avoided conflicting or contradictory messages between these two interventions, for instance, not using pain relief as the guide and threatening words such as “pain” during knee joint mobilization[14]. In addition, key messages of PNE were adapted to elderly patients in order to make it more easily understood[14].

PNE was provided in accordance with published guidelines[41]. Educational information was presented verbally and visually with the aid of a computer. The content and pictures presented in the sessions were based on the book *Explicando el dolor*[42] and a booklet designed for patients having knee replacement surgery[43]. Topics addressed during the PNE sessions included the physiology of the nervous system with especial interest in the pain system, characteristics of acute versus chronic pain; how pain becomes chronic (plasticity of the nervous system, central sensitization, etc.); potential sustaining factors of central sensitization like emotions, stress, pain behaviour and cognitions; surgical experiences and environmental aspects affecting nerve sensitivity; and reconceptualization of postoperative pain after knee joint replacement[42,43] (Table 3).

Four sessions on pain neurophysiology were delivered. The first session was a longer session lasting 50 to 60 minutes whereas the second, third and fourth follow-up sessions lasted 20-30 minutes. After the first session, participants were asked to read *Explicando el dolor*[42] at home. During the second, third and fourth sessions the therapist answered questions that had arisen after the first session and reading the book, tailoring these sessions and emphasizing the topics that needed additional explanation.

Knee joint mobilization was applied using Mulligan's mobilization with movement following the protocol from Takasaki et al[16]. Mobilization with movement during active knee flexion and/or extension, depending on which was the limited/painful movements for each patient, was applied progressing from non-weight-bearing to weight-bearing positions[16]. All the mobilizations were performed for three sets of 10 repetitions and patients were asked to perform

self-applied mobilizations at home involving four series of 20 movement repetitions per day[16]. Home treatment adherence was recorded by means of a diary. The mobilization with movement techniques used in this study are described elsewhere[44].

Biomedical education with knee joint mobilization

Individuals assigned to this group received information regarding anatomy and biomechanics of the knee, and etiology, symptoms, recommended treatments and surgical procedure of KOA. That information was provided by the same physiotherapist performing PNE in the other group through visualization of several videos which were presented on a computer. No information about mechanisms underlying pain was included in order to establish a clear difference with information provided from the PNE. The total duration of education was the same as PNE. After the education, these participants received the same mobilization protocol as the other group, except that all the mobilization techniques were pain-guided.

Statistical analysis

Sample size

The required sample size was calculated using G*Power 3.0.18 Software. Analysis of variance (ANOVA) repeated measures, within-between interaction was used in the system with CPM as the primary outcome measure. The effect size for the CPM was considered at 0.25. The correlation between repeated measurements assumed was assumed in 0.5. Considering four measures in two treatment groups, the sphericity correction was determined at

0.5. We estimated a sample size of 44 participants with a statistical power of 0.95 and an alpha level of 0.05. Considering a possible loss to follow-up of up to 20%, a total of 53 patients with KOA were recruited.

Analysis

Descriptive statistics were used to describe the baseline characteristics of individuals in each group. Student's t-test or Mann-Whitney U-test (for continuous variables) and chi-square or Fisher exact tests (for categorical variables) were applied to determine if there were baseline differences between groups.

Temporal summation was calculated as the difference in percentage between the 10^{th} and the 1^{st} pain rating score before occlusion using the formula: ((Temporal summation10th temporal summation1st)/temporal summation1st)*100[45]. CPM was calculated as the difference between the 10th pain rating score before occlusion and the 10th during occlusion[29].

The PPT, CPM and temporal summation data and data from the self-administration questionnaires were examined for normality using the Kolmogorov-Smirnov test which confirmed the suitability of ANOVA.

In order to analyze the effectiveness of the two interventions, a per protocol analysis was performed. Analysis of variance (ANOVA) was performed for each of the patient-related outcomes. Three-way ANOVA was used to evaluate differences in PPTs, CPM and temporal summation. The between subject factor was treatment (experimental treatment, control treatment), with time (baseline, immediately post treatment, 1 month post treatment, 3 months

post-surgery) and location (lateral knee, medial knee, epicondyle) as within subject factors.

Data from the self-administration questionnaires were each analyzed with a two-way ANOVA with treatment (experimental treatment, control treatment) as the between-subject factor, and time (baseline, immediately post treatment, 1 month post treatment, 3 months post-surgery) as the within subject factor. In each case, significant differences revealed by ANOVA were followed by post-hoc Student-Newman-Keuls (SNK) pair-wise comparisons. The effect size was calculated as the Partial Eta Squared (η^2_p) when significant. An effect size of 0.01 was considered small, 0.06 medium and 0.14 large[46].

Statistical analyses were performed using SPSS 22 (SPSS INc, Chicago, IL, USA). The significance level was set at $p < 0.05$.

RESULTS

The participant flow and retention is depicted in Figure 1. A total of 44 participants were finally analyzed [experimental treatment (n=22); control treatment (n=22)]. All these participants completed the four treatment sessions including the home task performance of mobilizations with movement and reading of the book if allocated to PNE.

Baseline characteristics of both groups are presented in Table 1. There were no significant differences in baseline variables between the groups (all $p>0.05$).

Primary outcome: conditioned pain modulation

CPM scores differed across locations ($F=4.92$, $p=0.007$, $\eta^2_{p:}$ 0.02) and were significantly lower at both the lateral knee (SNK: $p<0.01$) and epicondyle (SNK: $p<0.05$) compared to the medial knee. Regardless of the location, there was an interaction between treatment and time ($F=4.66$, $p<0.01$, $\eta^2_{p:}$ 0.02; Figure 2). However, the only significant change was observed for the experimental treatment between baseline CPM value and the value measured 3 months post-surgery (SNK: $p<0.05$) with lower values of CPM noted 3 months after surgery. No other changes were observed for the experimental treatment and no statistically significant changes were observed for the control treatment.

Secondary outcomes: temporal summation & PPTs

Temporal summation did not differ across locations ($F=0.01$, $p=0.98$) and between groups ($F=0.00$, $p=0.99$). Moreover, temporal summation did not change over time ($F=1.17$, $p=0.31$) for either treatment (Figure 3). There were no interactions between treatment, time or location for temporal summation.

PPTs differed across locations ($F=18.28$, $p<0.0001$, $\eta^2_{p:}$ 0.06) with higher PPTs at the lateral knee compared to the medial knee (SNK: $p<0.01$) and epicondyle (SNK: $p<0.0001$) and higher values at the medial knee compared to the epicondyle (SNK: $p<0.0001$). PPTs did not differ between treatments but changed over time ($F=11.28$, $p<0.0001$, $\eta^2_{p:}$ 0.06). For both treatments there was a significant increase in PPTs at all locations immediately post treatment (percent change in PPTs averaged across all sites: experimental treatment: 40.6 ± 31.2%; control treatment: 27.3 ± 41.7%), at 1 month after treatment

(experimental treatment: 49.6 ± 30.3%; control treatment: 24.4 ± 34.2%) and at 3 months after surgery (experimental treatment: 53.4 ± 45.3%; control treatment: 17.1 ± 30.5%) compared to baseline (SNK: all $p<0.00001$, Figure 4). However, there was no significant change for either treatment between the time points of immediately post treatment, at 1 month after treatment and at 3 months after surgery.

Secondary outcomes: symptoms of central sensitization, knee pain and disability

Table 2 shows results from the questionnaire data at each measurement time. The CSI score improved over time with both treatments ($F=5.51$, $p<0.001$, $\eta^2_{p:}$ 0.09), with no significant difference between treatments ($F=0.80$, $p=0.49$). For both treatments, the CSI score did not change from baseline to immediately post treatment or 1 month post treatment (all SNK: $p>0.05$). However it was significantly lower with both treatments when measured 3 months post-surgery compared to baseline, immediately post treatment, and 1 month after treatment (all SNK: $p<0.05$). The percent change at 3 months compared to baseline was -37.3 ± 24.0% and -11.7 ± 80.1% for the experimental and control treatment, respectively.

The WOMAC total score decreased over time ($F=19.46$, $p<0.0001$, $\eta^2_{p:}$ 0.26) for both treatments but was not dependent on the interaction between treatment and time ($F=1.07$, $p=0.35$). For both treatments, the WOMAC score decreased 3 months post-surgery compared to baseline (experimental treatment: -58.3 ± 21.9%; control treatment: -38.6 ± 31.5%), immediately post

treatment and at 1 month after treatment (all SNK: $p<0.0001$). The WOMAC score was also lower for both treatments 1 month after treatment compared to baseline (SNK: $p<0.01$; experimental treatment: -24.6 ± 21.9%; control treatment: -9.7 ± 23.9%).

Secondary outcome: psychosocial variables

There was an interaction for the PCS score between treatment and time ($F=7.26$, $p<0.001$, $\eta^2_{p:}$ 0.11). For the experimental treatment, there was a significant reduction in the PCS 3 months post-surgery, immediately post treatment and at 1 month after treatment (all SNK: $p<0.001$) compared to the baseline scores. Whereas for the control treatment, PCS score were the same three months post-surgery as they were at baseline (SNK: $p=0.59$). The only reduction in PCS score with control treatment was noted at 1 month after treatment versus baseline and immediately post treatment (SNK: both $p<0.0001$), but by three months post-surgery the PCS score had returned to baseline values. Significantly lower values of the PCS were seen with the experimental compared to control treatment immediately post treatment and at 3 months post-surgery (all SNK: $p<0.01$).

The TSK-11, which was dependent on the interaction between treatment and time ($F=6.81$, $p<0.001$, $\eta^2_{p:}$ 0.11), also showed no improvement with the control treatment. However, the TSK-11 score decreased with the experimental treatment immediately post treatment, at 1 month after treatment and 3 months post-surgery (all SNK: $p<0.0001$) compared to baseline score. The TSK-11 score was also significantly lower 3 months post-surgery compared to

immediately post treatment (SNK: $p<0.05$). The reduction of the TSK-11 score with the experimental treatment resulted in significantly lower values compared to the control treatment immediately post treatment, at 1 month after treatment and at 3 months post-surgery (all SNK: $p<0.00001$).

DISCUSSION

This study showed that a pre-operative treatment combining PNE with knee joint mobilization did not produce any significant superior effect in CS measures, knee pain and disability compared to biomedical education plus knee joint mobilization in people with KOA, either before or after surgery. Greater improvements for the group that received PNE with knee joint mobilization group were observed for psychosocial variables related to pain catastrophizing and kinesiophobia, which confirms part of our hypothesis. This improvement in the experimental group was observed both before and after surgery. Regarding CS measures, only some CS correlates (i.e. widespread hyperalgesia, CSI score) achieved significant improvement after both interventions (all PPTs increased at all measurement time points, CSI improved three months after surgery), with no additional benefits for the experimental group. Other indicators of CS such as CPM and temporal summation did not change over time following either treatment or even the observed changes were not in the expected direction.

Central sensitization

A significant increase in local and remote PPTs was demonstrated both before and after surgery with both treatments with a moderate effect size.

However, as seen in Figure 4, these changes were only clinically meaningful [28] for the local PPTs, in particular from baseline to immediately post treatment. The increase in remote PPTs after both interventions may provide evidence of modulation of central pain mechanisms[3]. Our findings are consistent with previous studies using knee joint mobilization[8,9] or PNE[47] in isolation, where both a local and global increase of PPTs was demonstrated after treatment. In studies assessing knee joint mobilization[8,9], passive oscillatory mobilization techniques were applied and only immediate effects on PPTs were evaluated. The current study expands the knowledge regarding the neurophysiological effects of manual therapy techniques for KOA, by showing short and long-term peripheral and central modulatory improvements when using mobilization with movement techniques preceded by education, regardless of the type of education provided.

To our knowledge, this is the first time that CSI has been used in a trial as an outcome measure. A decrease in symptoms of CS, as reflected by lower CSI scores, was observed after both treatments at all measurement time points with a medium effect size. For both treatments, the CSI score was significantly lower when measured 3 months post-surgery compared to the other measurement time points. On the contrary, other variables related to CS did not change over time with either intervention, or the changes were in the opposite direction to our a priori hypothesis (i.e. CPM). Conflicting results on CS measures were also reported by Skou et al[13] who concluded that, when assessing treatment effects through multiple pain-related measures including CS, results may differ depending on what measures are being evaluated[13].

Our results regarding CPM differ with previous research showing an enhancement of CPM after knee joint mobilization[8] or PNE[19]. We found no enhancement of CPM after either intervention. Differences in the nature of the mobilization technique (mobilization with movement versus passive oscillatory mobilization[8]) may have accounted for this discrepancy. Passive oscillatory mobilizations might be a preferable option to activate descending nociceptive inhibitory pathways for KOA, either alone or in combination with other interventions such as PNE. In addition, unlike previous research[8,19], mobilization with movement was always combined with initial education in the current study.

Knee pain and disability

Measures related to knee pain and disability improved for both treatments at all-time points with large effect sizes, but no significant differences were observed between treatments. Compared to baseline, improvements in knee pain and disability for both groups (Table 2) were not only statistically significant, but also clinically meaningful[36] at one month after treatment and three months post-surgery. These results are important as function of people waiting for surgery is significantly worse than that of the reference population[48]. Previous research showed beneficial effects on pain and disability following knee joint mobilization[8,9,16,17] and biomedical education[49].

Psychosocial variables

Only the experimental treatment achieved significant improvements in psychosocial measures at all follow-up points compared to baseline, with overall medium effect sizes. In addition, changes observed in the TSK-11 were

clinically meaningful[40] immediately post-treatment and 3 months after surgery when compared to baseline. Our results are consistent with known favorable effects of PNE on decreasing catastrophism and kinesiophobia observed in other chronic pain populations[18-20,47]. In addition, the post-surgical benefits observed after pre-operative PNE are in line with other studies[20].

Pre-operative educational programs for KOA, as applied in the control group, are centered on a biomedical model and don't normally include a pain science education component. This type of education was ineffective atchanging psychosocial factors in people with KOA. One possible reason may be that threatening terminology, which is characteristic of this kind of education had elicited negative emotional responses.

Limitations

The main limitation of this study is the lack of a control group not receiving any pre-operative intervention and undergoing surgery which would have allowed us to compare the results of both interventions with the natural history of KOA. In addition, given the small sample size, definitive conclusions cannot be extracted so further replication in a bigger sample is warranted. The relatively small sample size may also be a potential reason for the non-significant differences found for some variables.

The per protocol analysis may have introduced bias as participants who underwent surgery earlier were not included in the analysis. Minimal clinically important difference was only established for some variables, but not for others. Therefore, firm conclusions about clinical relevance of findings related to the variables where no data existed could not be made.

It is important to note that knee joint replacement surgery, when used alone, is an intervention capable of modulating CS and decreasing pain and disability in subjects with KOA[12]. It cannot therefore be discarded that the improvement observed in some measures of CS after surgery (i.e. CSI score) was due to the surgery itself and not to the tested treatments.

Due to the multimodal setup of the two interventions investigated, it is not possible to determine individually the efficacy of each treatment. In addition, treatment was not matched to pain phenotype of the participants when they entered the study. Individuals with a higher degree of CS might have responded better if assigned to the experimental treatment, as PNE is especially indicated when the clinical picture is dominated by CS[18,41]. Future studies could define subgroups of people with KOA having similar pain phenotype and evaluate whether matching interventions to subgroups results in improved outcome.

In conclusion, a pre-operative treatment for people with KOA combining PNE with knee joint mobilization did not produce any additional benefits in knee pain and disability and CS measures, when compared to biomedical education with knee joint mobilization. Superior effects were observed in the PNE and knee joint mobilization group for psychosocial variables related to pain catastrophizing and kinesiophobia.

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FIGURE LEGENDS

Figure 1. Participants flow and retention.

Figure 2. Mean ± SE of conditioned pain modulation at baseline, immediately post-treatment, 1 month post treatment and 3 months after surgery for individuals with knee osteoarthritis performing pain neuroscience education with knee joint mobilization versus subjects receiving biomedical education with knee joint mobilization. *: indicates significantly lower CPM values measured 3 months post-surgery relative to baseline ($p<0.05$).

Figure 3. Mean ± SE of temporal summation of pain at baseline, immediately post-treatment, 1 month post treatment and 3 months after surgery for individuals with knee osteoarthritis performing pain neuroscience education with knee joint mobilization versus subjects receiving biomedical education with knee joint mobilization.

Figure 4. Mean ± SE of the pressure pain thresholds at baseline, immediately post-treatment, 1 month post treatment and 3 months after surgery for individuals with knee osteoarthritis performing pain neuroscience education with knee joint mobilization versus subjects receiving biomedical education with knee joint mobilization. *: indicates a significant difference in PPT immediately post treatment, at 1 month after treatment and at 3 months after surgery compared to baseline ($p<0.00001$).