How much is needed? Comparison of the Effectiveness of Different Pain Education Dosages in Patients with Fibromyalgia

Objective: To assess the effect of different dosages of pain neuroscience education (PNE) programs on central nociceptive processing in patients with fibromyalgia. Secondly, to compare the effects of different dosages of PNE programs on numerical pain rating scale (NPRS), disability and psychological variables.

Design: Single-blind randomized controlled trial**.**

Setting: Three fibromyalgia centers in Spain (Valencia, Alcorcón, Alcalá de Henares).

Subjects: 77 patients with fibromyalgia.

Methods: Participants were randomized to four groups of PNE: (1) High Dose PNE, (n=20), (2) Low Concentrated dose PNE, (n=20); (3) Dilute Low Dose PNE, (n=20); (4) Control Treatment, (n=17) conducted in two 30-50 minute sessions in groups of 4 to 6 participants. Conditioned Pain Modulation (CPM), Temporal Summation (TS) and Pressure Pain Thresholds (PPT´s) were assessed at baseline and at 3-months follow-up. Secondary outcome measures were the Fibromyalgia Impact Questionnaire, Pain Catastrophizing Scale and the Pain Anxiety Symptoms Scale.

Results: There were significant between-group differences for NPRS in favour of the groups receiving High dose PNE, with a large effect size at 3-months follow-up (*p<0.01, η 2p: 0.170), but* there were not significant differences between groups for the rest of variables (p>0.05). All groups improved for central nociceptive processing, psychological variables, disability and pain intensity (NPRS).

Conclusions: Higher dosages of PNE produced a superior decrease in pain intensity at 3-months follow-up than other dosages of PNE and biomedical education. However, PNE regardless of the dosage did not produce superior effects on central nociceptive processing, disability or psychological variables as compared to biomedical education.

Keywords: Fibromyalgia Syndrome, Pain Neurophysiology Education, Diffuse Noxious Inhibitory Control, Central nociceptive processing.

INTRODUCTION

Fibromyalgia (FM) is a highly prevalent disease that affect 2-5% of the general population [35]. The characteristic clinical features of FM include diffuse stiffness and pain, fatigue, sleep disturbance and widespread mechanical and thermal hyperalgesia [9]. Patients with fibromyalgia present an impaired quality of life related both to specific musculoskeletal conditions and to general health [34]. The presence of nonspecific widespread pain may be related with mental health conditions as well [7]. Although the exact etiology of FM is currently unknown, peripheral and central nervous system related mechanisms seem to be involved in the development and perpetuation of pain [40-42]. Indeed the experience of pain in FM results mainly of a multifactorial phenomenon attributed to functional changes in the central nervous system [31]. The latter include impaired descending nociceptive inhibitory pathways (Conditioned Pain Modulation (CPM) paradigm of pain inhibits pain) and enhanced pain facilitatory pathways (paradigm of pain increase the pain) [22].

Compelling evidence of malfunctioning in the descending nociceptive inhibitory pathways in patients with FM comes from studies using CPM as an outcome measure [16,21]. CPM is paradigm of pain inhibits pain). For instance, inducing ischemic pain by means of the tourniquet test resulted in an increase of pressure pain thresholds (PPTs) in healthy controls, but not in FM patients [19]. Similarly, an enhancement of descending facilitatory pathways was shown in studies reporting an increase temporal summation (TS) in FM patients compared to healthy controls [40]. The augmented sensitivity (temporal summation) to pain in FM may partly be due to enhanced neural activity [14], a brain region involved in the affective/emotional modulation of nociceptive processing [39].

In order to address the affective/emotional modulation of nociceptive input, pain neuroscience education (PNE) can be used as part of the treatment of patients with chronic pain. It allows patients to improve and reconceptualize their understanding of (the origin of) pain, and therefore change negative beliefs and incorrect pain cognitions [30]. Two systematic reviews conducted by Louw et al. (2016) found that PNE decreased pain, disability and catastrophizing and improved physical functioning, beliefs and attitudes toward pain in patients with chronic musculoskeletal pain [24]. However, another recent systematic review also concluded that there is strong evidence about the effectiveness of patient education combined with other therapies in the short, medium and large term on pain, but not for improving functionality and disability in patients with FM [12]. Specifically for the treatment of FM the European League against Rheumatism (EULAR) recently published evidence-based

recommendations where the strongest evidence in the initial treatment of patients with FM, among all analyzed therapies, was for patient education and exercise. [25].

Furthermore, two previous studies have investigated the effects of PNE in people with FM using the CPM paradigm next to the effects on, pain intensity, disability and psychological variables as outcome measures [45,46]. One of them applied two face-to-face PNE sessions [46] whereas the other one used written educational material only [45]. From those studies, it can be concluded that two face-to-face PNE sessions, but not written educational material, is effective for down-modulating central sensitization and improving pain intensity, disability and psychological variables in people with FM [45,46]. And on the other hand the biomedical model of patient education (education that focuses on biomechanics, patophysiology) not has demonstrated to be effective, but also has shown a increase of anxiety and fear in patients who undergoing spinal surgery [36].

Possibly, inconsistencies in results might be caused by differences in dosages. Therefore, more work is needed to inform clinicians on the required dosage for providing effective PNE to patients with FM. For instance, it remains to be examined whether two face-to-face PNE sessions is the optimal dosage, or whether more PNE sessions will generate a larger effect on central nociceptive processing, pain intensity, disability and psychological variables in patients with FM?

For the reasons outlined above, the primary aim of this study was to compare the effects of different dosages of PNE versus biomedical education (because is the more usual intervention included in the clinical practice) on indices of central nociceptive processing, like CPM, TS and PPTs in people with FM. The secondary aim was to investigate the effectiveness of different dosages of PNE on pain intensity, Impact of FM on Daily Life and psychological variables in patients with FM. We hypothesized that PNE in its different dosages would result in significantly larger improvements in CPM, TS and PPTs factors than biomedical education and also PNE would improve pain intensity, FM impact and psychological variables better than biomedical education.

METHODS

Study design

A four-arm, parallel groups, assessor blinded, randomized controlled trial conforming to Consolidated Standards of Reporting Trials (CONSORT) guidelines [28] was performed between October 2013 and January 2016, at three FM centers in Spain (Valencia, Alcorcón, Alcalá de Henares). The study was approved by the Human Research Ethics Committees of the involved researchers' institutions and conducted in accordance with the Declaration of Helsinki. The study was registered at ClinicalTrials.gov (Trial Registration NCT02474875).

Participants

All potential participants were referred from three Spanish FM associations (Valencia, Alcorcón, Alcalá de Henares). Participants were selected if they met the following inclusion criteria: (a) fulfilled the 1990[48] and 2010[47] American College of Rheumatology classification criteria for FM; (b) reported an average pain intensity ≥ 4 on a 0 to 10 cm visual analogue scale during the previous week to study commencement; (c) were on stable doses of medication for FM ≥ 4 weeks; and (d) were aged between 18 and 65 years. Patients were excluded if: (a) suffered from an inflammatory rheumatic condition (rheumatoid arthritis); (b) had a planned surgery during the study period; (c) henced symptoms of bipolar disorder, major depressive disorder, panic disorder, or psychosis; and (d) did not speak Spanish fluently. Inclusion and exclusion criteria were selected from previous trials with FM patients [2,46]. Subjects were informed about the procedures and provided written informed consent prior to participation in the study.

The sample size was calculated using G.Power 3.1 software (University of Düsseldorf). Analysis of lineal general model of repeated measures (ANOVA), within-between interaction was used in the system with CPM as the primary outcomes measure. The effect size for the CPM was considered at 0.25. The correlation between repeated measurements was assumed in 0.5. Considering four measures in two treatment groups, the sphericity correction was determined at 1. It´s determined a sample size of 60 participants divided into 4 groups with a statistical power of 95%, accepting an alpha error of 0.05. Considering a possible loss to follow-up of up to 20%, a total of 72 patients with FM were required.

Procedure

Participants first recorded entered during a week their daily pain scores on a pain diary during the prior week. They then completed at the baseline assessment (4/10 pain intensity in NPRS). Three physiotherapists, specifically trained in all aspects of the assessment, were responsible for all the measurements. These assessors were blinded to the questionnaire data and treatment allocation. At three months-follow up the assessment was repeated. Every outcome was measured at baseline and at three months follow-up. All participants were instructed to continue current medication but not to start new medication or initiate new treatments during the study period.

Interventions

Participants were randomly allocated in one of four groups receiving different educational programs: (a) High Dose of PNE: six 45-minute sessions (PNE_HD); (b) Low Concentrated Dose of PNE: two 45-minute sessions) (PNE_CLD); (c) Dilute Low Dose of PNE: six 15-minute sessions) (PND_DLD); and (d) Control Treatment: two 45-minute session of biomedical education (BIOMED_ED).

The researcher administering the randomization schedule was different from those who recruited the participants. All the subjects were informed that they were participating in a study in which four different educational programs were compared. However, they did not receive any detailed information neither about the study design nor the interventions in terms of control or experimental groups. All interventions were applied at the three centres of FM associations by physiotherapists experienced in providing PNE. These therapists were different from those performing the assessments and thereby they were blinded to the results of measurements. All participants were instructed to continue to take any current medications but not to start new medications or initiate new treatments during the study period.

The contents covered by the PNE sessions were the same for the three intervention groups but adapted to the different durations assigned for each group and were provided in accordance with published guidelines [32]. A PowerPoint presentation was used for the PNE sessions addressing the following topics: physiology of the nervous system with special interest in the pain system, characteristics of acute versus chronic pain, the purpose of acute pain, how acute pain originates in the nervous system (nociceptors, ion gates, neurons,

action potential, nociception, peripheral sensitization, synapses, synaptic gap, inhibitory/excitatory chemicals, spinal cord, descending/ascending pain pathways role of the brain, pain memory and pain perception), how pain becomes chronic (plasticity of the nervous system, modulation, modification, central sensitization, the pain neuromatrix theory) and potential sustaining factors of central sensitization like illness, emotions, stress, perceptions, pain cognitions and pain behaviour [32]. The differences between the PNE groups were not in the above-mentioned contents but in the time available to explain them, therefore in the administration of the information and, consequently, in the rhythm in which the patients assimilated it. The information was presented in an understandable way by patients using pictures, examples, and metaphors. During the educational sessions, it was also explained why and how various treatment components (i.e. graded activity and exercise therapy) are likely to contribute to decreasing the hypersensitivity of the central nervous system (26). In addition to formal PNE sessions, all participants were asked to read at home *Explicando el dolor* book [6]. This written information did not provide new information but only reinforced the verbal information provided in the formal PNE sessions. All PNE education groups are explained to all the points just mentioned.

After each session, the therapists answered questions that had arisen after that PNE sessions and reading the book. Patients were also asked if they had tried to apply what they had learned during the education sessions in their daily life and what their experiences were. In the final part of the sessions, patients were motivated and coached to apply their new insights into their daily life.

Outcome Measurements

The primary outcome measures was the degree of TS, PPT and the efficacy of CPM. Secondary outcomes were questionnaires assessing pain intensity, disability (Fibromyalgia Impact Questionnaire) and psychological variables (catastrophizing and pain anxiety). All the outcomes were measured at baseline and at three months follow-up after finished the treatment.

Primary Outcome Measure

Indices of central nociceptive processing: PPT, TS, CPM

Firstly, baseline *Pressure Pain Thresholds (PPTs)* were assessed using algometry in the thumb (dorsal aspect of the distal phalanx). The PPT is defined as the lowest pressure that, using standardized testing conditions, needs to be applied to cause the slightest sensation of pain. It is a reliable and widely used measure [38]. The PPT is defined as the lowest pressure that, using standardized testing conditions, needs to be applied to cause the first sensation of pain [43]. It is a reliable and widely used measure [33]. The PPT was measured using an analogue Wagner algometer (Wagner Instruments, Greenwich, CT) with a surface area of 1 cm^2. The algometer probe tip was applied at a rate of 1kg/cm^2/s and the average of three consecutive measurements, applied every 30 seconds, was used for analysis. PPTs are a reliable and widely used measure mechanical hyoeralgesia [33].

Two minutes after PPTs, to avoid carry over effects, TS and CPM were measured as described by Cathcart et al. [8] and previously used by others (24)

The degree of *TS or wind-up* was evaluated in response to 10 applications (pulses) of the algometer, with an approximate rate of pressure increase of 2 Kg/s, at the previously defined PPT at the dorsal surface of the right-hand middle finger midway between the first and second distal joints, and at the middle of the right-hand side upper trapezius belly. Participants were asked to rate the intensity and unpleasantness of the pain intuitively of the first, fifth, and tenth pulse on a numeric pain rating scale (NRPS) (0 = no pain to 10 = worst possible pain). The degree of TS, reflecting the degree of pain facilitation, is calculated as previous study [23].

After an interval of 5 minutes, *CPM* was assessed by replicating the TS assessment associated with a conditioning stimulus for eliciting CPM. The conditioning stimulus was an occlusion cuff at the left arm inflated, at a rate of 20 mmHg/s until the subject reports "the first sensation of pain". Acquired pressure at this point remained for 30 seconds. The subject described the intensity of pain, because of occlusion in the arm, on a verbal numerical rating scale (0 = no pain and 10 = worst possible pain). Then cuff inflation was increased or decreased until the intensity of pain will be 3/10 in verbal rating scale. The TS procedure described above was repeated with the cuff inflated and the arm relaxed. The efficacy of CPM, reflecting the efficacy of endogenous pain inhibition, was calculated as previous studies. In healthy controls CPM induced by the ischaemic cuff can dampen TS [8]. The same method was previously used in, chronic fatigue syndrome, FM and rheumatoid arthritis [26]

Secondary Outcome Measures

Impact of FM on Daily Life

The FIQ, which is a validated self-reported questionnaire to measure multidimensional function/health-related quality of life, was used (25). Scores in the FIQ range from 0 to 100, with higher scores indicating lower quality of life. Average FM patients score around 50 points and severely affected patients >70 points[5]. An improvement greater than 30% in the FIQ total score has been identified in clinical trials as sensitive to identify a positive response to treatment [3].

Pain Catastrophizing

The Spanish version of the Pain Catastrophizing Scale (PCS) was used to assess catastrophic thoughts about pain, which has shown appropriate psychometric properties [13]. It has been sugessted that the cutoff score to consider a clinically level of catastrophzing indicates a score of 30 over a total of 50 points [44].

Pain Anxiety

The Pain Anxiety Symptoms Scale-20 (PASS-20) was used to evaluate symptoms associated with anxiety. The questionnaire It consists of two subscales (PASS-1 and PASS-2). This questionnaire has good psychometric properties[1,37]. Also the Spanish version used in this study also showed goodpsychometric properties[20]. Has been suggested that the cutoff to consider be indicative of high levels of pain-related anxiety is when in a PASS-20 total score exceeding 30 points [1].

Pain intensity

Pain intensity was measured with the NRS of 11 points (interval from 0 to 10), where 0 corresponds to no pain, and 10 corresponds to the worst pain imaginable. A graphical representation of 11 spaces was used to indicate the patient's own evaluation of his or her pain. The patients were asked to assess the subjective pain intensity of the painful in whole body by pointing with one of their fingers to mark the level of pain on the scale. The NRS is a valid and reliable tool and its correlation with the VAS shows a high convergent validity (0.79–0.95) [17]. The minimal detectable change (MDC) for the NRS was established in 2 points [10] and a minimal clinically important difference (MCID) in knee osteoarthritis pain intensity [18].

Randomization

Participants were randomly allocated using a computer-generated random-sequence table with a two-balanced block design (GraphPad Software, Inc. CA 92037 USA) by an independent researcher who was not involved in the recruitment, assessment or treatment of the subjects.

In all groups participants were informed that they were participating in a study in which they were randomly allocated in one of four groups of educational programs to be compared. They did not receive any information about the design and the interventions in terms of control or experimental groups.

Statistical analysis

Statistical analyses were performed using SPSS version 20.0. The Kolmogorov-Smirnov test was applied to determine if there were baseline differences between groups. To analyze the effectiveness of the four 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 TS. The between subject factor was treatment (BIOMED_ED group, PNE_ HD group, PNE_ CLD group, PNE_ DLD group), with time (baseline, immediately post treatment, 3 months follow-up) and location (finger, trapezius) as within subject factors. Data from the self-administration questionnaires were each analyzed with a two-way ANOVA with treatment (BIOMED_ED group, PNE_ HD group, PNE_ CLD group, PNE_ DLD group) as the between-subject factor, and time (baseline, immediately post treatment, 3 months follow-up post treatment) 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 ($\eta^2 p$) when significant. An effect size of 0.01 was considered small, 0.06 medium and 0.14 large[15]. The results are presented with a 95% confidence interval (CI) for all the variables. The significance level was set at $p<0.05$.

RESULTS

One hundred and twelve patients with FM were screened for eligibility. A total of 77 patients fulfilled the inclusion criteria and successfully completed the study. The participants had a mean age of 53.40 ± 9.08 years (mean ± SD), a mean weight of 66.44 ± 11.51 kg, and a mean height of 1.61 ± 6.08 m. Seventeen patients completed the study in the BIOMED_ED group (1 male, 16 females; mean age ± SD, 50.15 ± 10.53y), 20 in the PNE_ HD group (3males, 17 females; mean age ± SD, 54.33±10.98y), 20 in the PNE_ CLD group (20 females; mean age ± SD, 55.47±8.59y) and 20 in the in the PNE_ DLD group (2 males, 18 females; mean age ± SD, 49.31 ± 6.87y). Figure 1 shows the participant flow and retention. Baseline characteristics of the four groups are presented in Table 1. The one-way ANOVA showed no statistically significant differences at baseline in age, weight and height between the groups ($p>.05$). Chi square test showed no statistically significant differences at baseline in sex ($p>.05$).

Primary Outcome:

Conditioned Pain Modulation

There were no significant changes for the interaction between treatment group and time and location ($F=0.383$, $p>0.05$, η^2p: 0.018; Figure 2). Also, there were no significant changes for the interaction between treatment group and time ($F=1.012$, $p>0.05$, η^2p: 0.045; Figure 2). However, CPM changed over time improvement ($F=6.948$, $p<0.01$, η^2p: 0.098; Figure 2) for all treatment groups. There were no significant differences in CPM scores across locations ($F=2.570$, $p>0.05$, η^2p: 0.039).

Temporal summation

TS did not change over time ($F=2.828$, $p=0.063$, η^2p: 0.042). However, TS did not differ between groups ($F=0.343$, $p>0.05$, η^2p: 0.0 16; Figure XX). Finally, there were no significant differences between locations ($F=2.636$, $p=0.109$, η^2p: 0.040) (Figure 3). There were no interactions between treatment, time or location for TS.

PPTs

Statistically significant differences were observed in PPTs across locations ($F=201.116$, $p<0.0001$, η^2p: 0.761). PPTs did not differ between treatments ($F=0.890$, $p>0.05$, η^2p: 0.041)

but changed over time (F=11.178, p<0.0001, η^2p: 0.151). For all treatments there was a significant increase in PPTs at all locations immediately post-treatment assessment (percent change in PPTs averaged across all sites: Biomedical education group: 0.74 ± 29.81%; PNE_ HD group 0.34 ± 17.13 %; PNE_ CLD group: 0.66 ± 25.64 %; PNE_ DLD group: 0.72 ± 27.06%) and at 3 months after treatment (percent change in PPTs averaged across all sites: Biomedical education group: 0.46 ± 18.82 %;, PNE_ HD group 0.37 ± 18.59 %, PNE_ CLD group : 0.35 ± 13.63 %; PNE_ DLD group: 0.024 ± - 0.75%) compared to baseline (SNK: all p<0.00001, Figure 4). There were no interactions between treatment, time or location for mechanical hyperalgesia (p>.05).

Secondary outcomes:

Pain intensity

There was an interaction for pain intensity between treatment and time (F=3.081, p<0.01, η^2p: 0.170). For PNE_HD group, the pain intensity significantly (P<0.001) decreased 3 months follow-up post-treatment compared to baseline (BIOMED_ED group: -0.67 ± 7.95%; PNE_ HD group – 1.77 ± 26.33 %, PNE_ CLD group: - 0.04 ± 0.56%; PNE_ DLD group: - 0.95 ± 12.08%). For the rest of treatment groups the pain intensity decrease was not statistically significant (SNK p>.05). However, pain intensity decreased over time (F=10.201, p<0.0001, η^2p: 0.185) for all treatment groups (Table 2). Recommendations for determining clinically important changes for outcome measures in chronic pain trials indicated that a decrease of two points over 10 or a 30% reduction in pain intensity, as measured with a NRPS, are considered moderately MCID. In our study PNE_HD reached 26.4% of the recommended minimally detectable change [11].

Impact of FM on Daily Life

The FIQ score decreased over time (F=4.367, p<0.05, η^2p: 0.068) for all treatment groups, but was not dependent on the interaction between treatment and time (F=0.558, p>0.05, η^2p: 0.027). The FIQ score was lower for all treatment groups 3 months after treatment compared to baseline (p<0.05; BIOMED_ED group: -4.30 ± 6.05%; PNE_ HD group: -6.71 ± 11.55%; PNE_ CLD group: -9.78 ± 15.91%; PNE_ DLD group: -9.70 ± 16.10%). Table 2 shows results from the questionnaire data at each measurement time. Previous studies have established the minimal detectable change for the FIQ and have found that a 14% change is clinically

relevant[4]. In our study only the PNE_CLD PNE_DLD of PNE reached a 15.90% and 16.08% change in the FIQ score, respectively.

Pain Catastrophizing

There was an effect for time factor in all the treatment groups for the PCS score (F=9.417, p<0.001, η^2p: 0.132). However, there was no interaction between treatment and time (F=2.065, p=0.062, η^2p: 0.091). For the PNE_ CLD group there was a higher reduction in the PCS immediately post treatment and at 3 months, with a 19.90% and 21.96% of improvement respectively compared to the baseline scores. The group that had greater improvements in the PCS was BIOMED_ED with a reduction in the PCS of 18.61% immediately post treatment and 14.79% at 3 months,whereas the PNE_ HD group only reached a reduction of 12.72% in the PCS at 3 months and no improvement was observed for PNE_ DLD group.

Pain Anxiety

The 4x4 mixed model ANOVA showed statistically significant differences in the time factor (PASS-1: F=5.887; *P*<.01; η_p^2=0.087; PASS-2: F=3.244; *P*< .05; η_p^2=0.050) but not significant interaction between group and time (PASS-1 F=0.626; *P*=0.709; η_p^2=0.029; PASS-2 F=0.882; *P*=0.510; η_p^2=0.041). (Table 2).

DISCUSSION

This study showed that both PNE (regardless of different dosages) and biomedical education produces similar significant improvements on conditioned pain modulation and mechanical hyperalgesia (e.g. increase in PPTs), in pain catastrophizing and pain anxiety in patients with FM. No effects were observed in temporal summation with either intervention. In addition, a higher dosage of PNE (6 sessions of 45 minutes) produced superior effects on pain intensity than lower dosages of PNE (2 sessions of 45 minutes or 6 sessions of 15 minutes) and biomedical education in this population.

Central nociceptive processing measures

Regarding CPM, PPT and TS do not match with those of a previous study [46], where two one-to-one PNE sessions provided to patients with FM were more effective for improving CPM, PPT and TS than a control group with self-management techniques. However, in a recent study where PNE was combined with manual therapy and compared to biomedical education plus manual therapy in patients with knee osteoarthritis, authors found similar effects in these three variables in both groups [23], which is in agreement with our results. The causes that can may explain these discrepancies between studies is because a combination of treatment were applied in comparation with our study that we have done a single treatment. Based on the results of the current study and previous research (17), it seems that patient education regardless of the dosage and the type of education (PNE vs biomedical) might be an option to enhance endogenous pain inhibition in patients with FM. Future studies should confirm these preliminary findings.

Impact of FM on Daily Life

Two previous studies using PNE in patients with FM used the FIQ as an outcome measure with contradictory results. In one study, two sessions of PNE produced an improvement in the impact of FM on daily life [46], but in another one there were no positive effects on disability when applying PNE in a written format to women with FM [45]. In the van Oosterwijck's study [46] the effect size of PNE was high whereas we found a medium effect size.

Psychological variables

A systematic review concluded that PNE decrease pain catastrophizing in patients with chronic musculoskeletal pain [24]. In this study a decrease on pain catastrophizing and anxiety of pain was observed in all the groups (Table 2). These findings are in accordance with a previousstudy using PNE for patients with FM [46]. Other studies performed in patients with chronic fatigue pain syndrome have demonstrated a reduction of pain catastrophizing.[27]. However, others have shown that PNE produce superior effects than biomedical education in pain catastrophizing when is applied to patients with knee osteoarthritis. In addition, when PNE is performed in a written format no effects were observed in pain catastrophizing in patients with FM. [45].

Pain intensity

Although pain intensity decreased in all groups, a significantly higher improvement was observed with higher doses of PNE. The decrease in pain intensity we found was superior than that reported in a previous study using also PNE in patients with FM [45]. On the other hand, the other study using PNE in FM [46] did not measure pain intensity. Compared with studies where PNE was used for patients with low back pain, our improvement in NPRS (e.g. 1.77 points in the high dosage PNE) was superior to that reported by Moseley et al [29].

Clinical implications and future studies

The results of the present study have clinical implications since it confirms that educating FM patients improves the measures of central sensitization, disability and psychological variables. In addition, these education sessions can be carried out in groups, with the consequent saving of economic and human resources compared to individual treatments. Another clinical implication is that when it comes to educating patients we must take into account the "dosage", that is, the rhythm at which the new concepts are introduced and the time given to teach and to assimilate the concepts taught. Compared with biomedical education, the PNE applied with higher doses should be used preferably since it improves its clinical effectiveness generating a greater decrease in the pain intensity in the medium term (3 months).

Future work should examine whether different dosages of PNE education affects the observed effects and if the effects remain at long-term (e.g. 6, 12 and 24 months follow-up).

Limitations and strengths

The first limitation of this study is the absence of a control group receiving no treatment. This would have allowed us to compare the effects of the different interventions with the natural history of FM. However, we considered unethical not to educate patients with FM about their condition and therefore chose not to include a control group not receiving any education. Secondly, the effect of the interventions was not assessed beyond the 3 months follow-up period. Third, the recruitment was done by the reserachers involved in the study who contacted with the patients. This fact might have influenced the patients' expectations for care as well as the selection of the most motivated patients. Forth, baseline educational level of the participants was no recorded. Finally, the educators were not blinded to treatment allocation, but given the nature of the treatment (i.e. patient education), blinding the therapists was not possible.

To our knowledge this is the first study comparing different dosages of PNE in the treatment of patients with (chronic) in general, and patients with FM in particular.

CONCLUSION

Different dosages of PNE vs biomedical education did not produce superior effects on central sensitization measures, disability and psychological variables, but higher dosages of PNE produced a higher decrease in pain intensity than other dosages of PNE or biomedical education in patients with FM at 3 months follow-up post-treatment.

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