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Study of the mechanisms of action of the hypoalgesic effect of pressure under shock waves application: A randomised controlled trial

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ABSTRACT

Objective: To determine if the perceived pain intensity during the application of shock waves (SWs) is a determinant mechanism in producing hypoalgesic changes in pressure pain thresholds (PPTs) in asymptomatic individuals.
Design: A randomised, single-blind controlled trial [NCT03455933].
Setting: University.
Participants: Sixty-three asymptomatic individuals.
Interventions: Participants were randomised into three groups: 1-SWs causing mild pain (SW-DP); 2-SWs generating moderate pain (SW-MP); and 3-cold pressor test (CPT).
Main outcome measurements: Before and after the intervention, the PPT was evaluated bilaterally at the following points: lateral epicondyle, median nerve in the flexure of the elbow, and tibia.
Results: The results showed differences between various groups over time for all PPTs assessments, due to the existence of statistically significant differences in the interaction group x times (dominant arm lateral epicondyle [$P < 0.001$; $\eta^2p = 0.255$]; dominant arm median nerve [$P = 0.001$; $\eta^2p = 0.212$]; nondominant arm lateral epicondyle [$P < 0.001$; $\eta^2p = 0.275$]; nondominant arm median nerve [$P < 0.001$; $\eta^2p = 0.268$]; tibia [$P = 0.012$, $\eta^2p = 0.138$]). The SW-MP group obtained a significant increase in all the PPT evaluations compared with the SW-DP group ($d > 0.80$). The CPT group only showed significantly higher results, and of high magnitude ($d > 0.80$), regarding the SW-DP group for the PPT evaluation in the dominant member. The SW-MP group showed differences compared with the CPT only for the PPT obtained in the nondominant arm.
Conclusions: The findings show that SW treatment generates a hypoalgesic effect on the application point, with moderate pain. Further studies are necessary in order to link these hypoalgesic changes to the activation of the descending inhibitory systems.

1. Introduction

Extracorporeal shock waves (SWs) are longitudinal acoustic waves that may be propagated through water or soft tissues without losing a significant amount of their power.[1] Currently, two types of SWs are known, and they mainly differ in the scope of their effect at the tissue level: 1) radial waves (surface effect); and 2) focal waves (deep effect).[2] Regarding the treatment of musculoskeletal pathologies through SWs, the evidence shows that the results under radial SWs application are similar to those obtained with focal SWs.[2–6] However, in the specific case of lateral epicondylagias, it is common to use radial SWs due to their greater convenience of application and their extension across the area of treated tissue.[7,8]

The effectiveness of SW therapy for the treatment of tendinopathies is controversial, although it could currently be considered a reasonable option in the absence of more conclusive literature.[9–12] According to some studies, SWs are at least as effective as infiltrations and/or surgery for pain reduction and tendon recovery; thus, they could be an alternative to these interventions because it is a non-invasive treatment with lower risks.[12–14] In fact, the literature supports the use of SWs, given

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there is no evidence of the presence of secondary effects with its use if the contraindications for this technique are taken into account.[14,15]

The biological effect of SWs is hypothesised to be due to mechanotransduction effets, a phenomenon in which the mechanical action of ultrasonic vibrations on tissues leads to their regeneration and healing.[16–18] Currently, there are two main hypotheses regarding the probable analgesic effects produced by the treatment with SWs:[19] 1) SWs degenerate nerve fibres originating in small immunoreactive neurons, decreasing the concentration of pro-inflammatory mediators; 2) the second hypothesis is the theory of analgesia by hyperstimulation, which suggests that the application of SWs generates the release of endorphins and other analgesic substances by activating the descending inhibitory system. However, it is currently unknown precisely what mechanisms are responsible for the analgesic effect of SWs (2), which has been demonstrated by the evaluation of measures such as threshold to pressure and pain intensity, among others.[8,20–22]

Conditioned pain modulation is an experimental paradigm that examines the state of the descending inhibitory system function.[23,24] In a standard nociceptive system, the amount of pain experienced by a primary nociceptive stimulus will be reduced during/after the presentation of a second nociceptive stimulus due to the activation of endogenous analgesia.[23] Therefore, taking into account that the analgesic effect of SWs is more significant when the maximum energy density tolerable by the patient is applied,[25] we could suggest that the analgesic effect may be mainly due to activation of the descending inhibitory system.

Thus, we hypothesized that higher perceived pain intensity during SW stimuli may produce greater hypoalgesic effects in pressure pain thresholds (PPTs) of asymptomatic individuals. Indeed, the objective of this study was to assess whether the pain intensity perceived during the application of SWs was determinant in producing hypoalgesic changes in PPTs in asymptomatic individuals. In addition, we analysed whether a nociceptive stimulus of similar pain intensity, such as in the application of SWs with moderate pain, was equally effective in increasing the PPT, which could suggest that the analgesic mechanism underlying the technique could be the activation of the descending inhibitory system.

2. Methods

2.1. Study design

A single-blind, randomised controlled trial was performed, consisting of a total of three groups. The study was approved by the Research Ethics Committee of the La Salle University Studies Centre in Madrid, was developed according to the criteria established in the CONSORT statement,[26] and was registered in the United States Clinical Trials Registry (registration number: NCT03455933).

An independent researcher carried out a randomised assignment of the participants to the groups using the GraphPad Software (GraphPad Software Inc., La Jolla, CA, USA). In addition, the evaluator was continuously blinded to the intervention group received by each participant. In order to guarantee the blindness of the evaluator, the investigator who administered the intervention asked for the participants to avoid comments about the study. On the other hand, participants were not blinded, due to the difficulty to include a placebo in this type of intervention.

2.2. Participants

The participants were recruited from the university campus through posters and social media during May 2018. All individuals interested in participating in the study had to read and sign the study's informed consent document. Of these, all asymptomatic men and women (absence of pain or illness) between 18 and 40 years of age (early adulthood), without cognitive alterations and with fluency in both written and spoken Spanish, were included.

Excluded from the study were individuals who presented systemic diseases, tumours, infections, pacemakers, pregnancy, coagulation disorders, skeletal immaturity, fibromyalgia, history of whiplash, dizziness, or those who were receiving some sort of physiotherapeutic, pharmacological, or any other treatment. In addition, those participants who received SWs and did not reach the intensity of pain corresponding to their group with an energy equal to or less than 0.3 mJ/mm^2 (2 bar), were also excluded. This last criterion was determined based on previous literature that established that intensities greater than 0.3 mJ/mm^2 (2 bar) could produce vascular damage.[27–30] Furthermore, previous experience with SW therapy clinically was considered an exclusion criterion. Considering our research, three subjects were not enrolled into the study based on the following exclusion criteria: two of them were under physiotherapy treatment for low back pain and knee pain, and the other one had whiplash history.

2.3. Interventions

All the participants, regardless of the group to which they had been assigned, received a single treatment session. With the intention of avoiding possible confounding factors, all the interventions were applied to the dominant superior member of the participant. All the participants were informed that they could terminate the intervention at any time if they felt uncomfortable or for any other reason. Below is a detailed description of each of the interventions applied in this study.

2.3.1. Shock waves-mild pain (SW-DP)

This group was considered the control group. The administration of this intervention was performed using a portable SW device (SHOCKMASTER 300, Helios Medical, Madrid, Spain). According to the criteria recommended in systematic reviews for an optimal application of SWs,[31,32] a total of 2000 impulses were applied with a frequency of 8 Hz on the lateral epicondyle. The intensity selection was dependent on the severity of pain perceived by the participant. Specifically, the intensity of energy was progressively increased until the participant perceived a pain score from 1.5 to 2 on the Visual Analogue Scale (VAS); approximately 5–10 impulses were applied to each participant. It should be noted that the impulses were applied starting with an intensity of half energy (1 bar according to the Rompe classification,[30,33] which increased until reaching the mentioned objective or reaching 2 bar [high energy][30,33]).

After 5 min of identifying the appropriate energy intensity for each participant, application of the SWs was begun, with the previously determined intensity. During the application of the 2000 impulses, it was necessary for the participant to reach a score of 3/10 on the VAS. In addition, a maximum of two pauses (30 s each) was allowed if the participant reached this pain intensity, to avoid the perception of a higher pain intensity than the one pre-established for the intervention group.

2.3.2. Shock waves-moderate pain (SW-MP)

The participants assigned to this group received a protocol identical to the SW-DP group. The only difference was that the intensity of energy was established with the purpose of reaching a pain scale of 6/10 on the VAS. For this, the intensity of energy was calculated by increasing it until the patient perceived a pain ranging from 4.5 to 5 on the VAS. Indeed, considering the temporal summation of pain, the intensity for SWs application was selected obtaining a VAS score slightly lower than that established for each group. Thus, the pain intensity corresponding to each group would be reached without having to stop more than 2 times to apply the 2000 impulses.

2.3.3. Conditioned pain modulation (CPT)

This group received the application of the cold pressor test (CPT). For this, the participants were asked to submerge their dominant hand,

held completely open up to the wrist, inside a container full of water at a temperature of 1 °C, which was maintained with ice. It should be noted that the container was separated into two different compartments using a plastic mesh to avoid direct contact of the ice with the participant's hand.[23] According to the literature, the maximum duration of this test should not exceed 2 min.[34] Therefore, the test was terminated upon reaching 2 min of immersion or when the patient reached a score of 6/10 on the VAS.

Considering all interventions, the application time varied slightly between participants depending on the number of pauses (a maximum of two pauses with 30 s for each pause), due to the intensity of pain for each group had been reached, however, in general the average time of the application was 4–5 min. The appropriate intensity calculation was performed before the intervention started by the application of 5–10 impulses. After 5 min of the intensity application identification, the respective intervention was then applied. Taking to account that only 5–10 impulses were applied with 5 min of rest, the authors considered that the conditions at the beginning of the intervention were similar. In addition, the activation of the descending inhibitory system during the procedure of the intensity selection should be similar to the obtained in this group due to the stimulus was based on the pain intensity for the corresponding group (mild or moderate). Thus, the CPM would continue to be assessed for pain intensity mild or moderate. The duration of the 2000 impulses application ranged 4–5 min depending on the possible breaks performed (maximum of two pauses of 30 s). Finally, the pain stimuli, despite being of equal intensity, was maintained over more time during the application of SWs (4–5 min approximately) compared to the application of CPT application (maximum 2 min). This aspect could be explained by the slight hypoalgesic superiority showed by the SW-MP group with respect to CPT group, based on a hypothetically higher activation of the descending inhibitory system.

2.4. Variables

2.4.1. Primary outcome: pain pressure thresholds

A digital algometer (FDX 25, Wagner Instruments, Greenwich, CT, USA) was used to measure PPTs by an experienced physical therapist (with more than 6 years of experience in musculoskeletal assessments).[35] This instrument contains a circular platform of 1 cm^2 through which a perpendicular pressure is progressively applied to the skin (at a velocity rate of 1 kg/s).[36] Before beginning the study, a prior PPT assessment training was performed in order to ensure an equal rate in pressure increase. The participant was asked to indicate the moment at which the pressure stimulus became painful. Then, the maximum score (kg/cm^2) marked at this moment was used for the analysis data as the highest PPT value that remained in the display. In each anatomical location three measurements were made, each spaced by 1 min of rest, using an average of three for the data analysis, the latter being expressed in kg/cm^2.[36–38] The reliability of this instrument has been widely demonstrated (intraclass correlation coefficient [ICC]: 0.91; minimum detectable change: 0.54 kg/cm^2).[39]

2.4.2. Secondary outcomes: control variables

Kinesiophobia and catastrophism were evaluated to control the possible influence of psychological factors on hypoalgesic changes, due to these outcomes may alter the results of the PPT and the ability to modulate pain.[40,41] Both psychological constructs were evaluated using the following scales, which are validated in Spanish and have acceptable psychometric properties: 1) the abbreviated version of the Tampa Scale of Kinesiophobia (TSK-11);[42] 2) the Pain Catastrophizing Scale (PCS);[43] and 3) The Hospital Anxiety and Depression Scale (HADS).[44]

2.4.3. Secondary outcomes: self-report variable

The VAS was used to measure the patient's pain intensity. This scale consists of a 10-cm horizontal straight line, whose limits correspond with the "absence of pain" and the "worst pain imaginable." In this investigation, the patient was asked to indicate on the line the point that best described his pain at the time of evaluation. A value lower than 4 in the VAS means mild or mild-moderate pain, a value between 4 and 6 implies the presence of moderate-severe pain, and a value greater than 6 implies the presence of a very intense pain.[45] The VAS has proven to be a reliable instrument in the evaluation of acute pain (ICC = 0.97).[46] Pain intensity was obtained by the VAS. The participant was blinded and not allowed to observe the scale numeric data value. The assessor showed the scale to the participant during the SW application (both for calculating the pain intensity selection and assessing the pain intensity during the intervention). The participant should indicate his/her pain intensity by moving the marker through the 10-cm horizontal straight line. Thus, The pain intensity was continuous assessed throughout the SW application, whereas the participant was blinded to the VAS numeric data value.

2.5. Procedure

Before beginning the study, the evaluators received specific training on the measurement protocols so that the assessments would present the minimum possible error. The therapists were trained in the application of the various interventions included in this study.

Once the participants consented in writing to their inclusion in the study, they were randomly assigned to the various intervention groups. Immediately afterwards, the participants went to an independent room, where participants self-reported the TSK-11, PCS, and HADS scales for their proper completion, and then the PPTs evaluation were performed in different locations. Specifically, the PPT was evaluated bilaterally in (1) the lateral epicondyle (Fig. 1); (2) the median nerve path at the level of the elbow (Fig. 2); and (3) in the tibialis anterior muscle (Fig. 3).

After the initial evaluation, the therapist directed the participants to the treatment room to apply the designated intervention. Finally, 5 min after the intervention, the PPT was re-evaluated in the same way as the pre-intervention measurement.

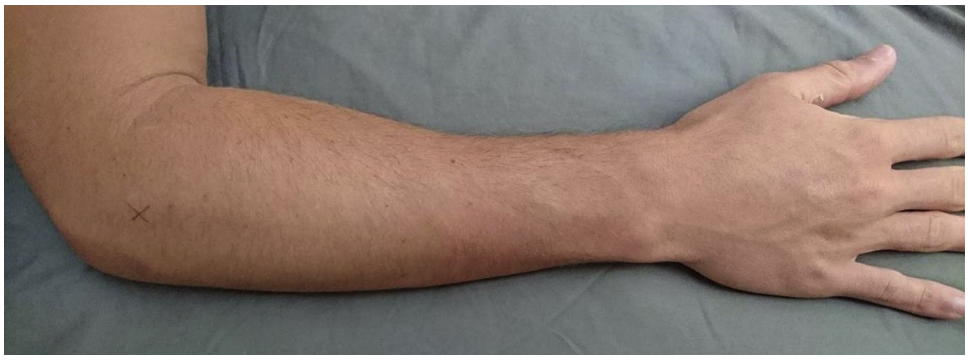

Fig. 1. Insertions of the extensor muscles of the elbow at the level of the lateral epicondyle.

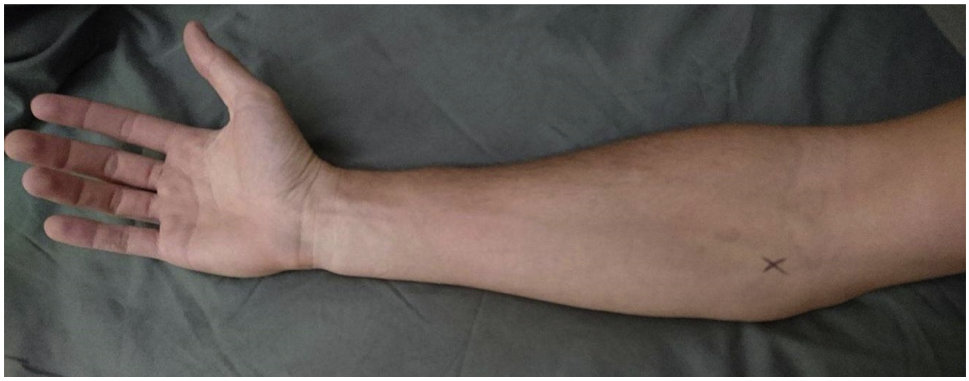

Fig. 2. Point of the path of the median nerve at the level of the elbow.

2.6. Sample size

The sample size was calculated with the G * Power 3.1.7 program for Windows (G * Power © by the University of Dusseldorf, Germany). With the intention of detecting differences between groups in the PPTs, an analysis of variance (ANOVA) of repeated measures, focused on the interaction group x time, was used as a statistical test. To our knowledge, there were not previous investigations similar to the present study; thus, the effect size was determined through a pilot study. Based on the results of this pilot study (30 participants, 10 per group), the tibia pressure was chosen for the size of the effect obtained for the pain threshold, given it was the least significant. Thus, with a moderate effect size (f = 0.25), a power of 90%, and accepting an alpha error of 5%, it was determined that at least 18 participants were required per group. Finally, we increased the sample size by 10% due to possible losses or dropouts during the intervention; therefore, the final size per group was 20 participants (60 participants in total).

2.7. Data analysis

The data analysis was performed using the statistical software SPSS (Statistical Package for the Social Sciences 21, SPSS Inc., Chicago, IL, USA). The Shapiro–Wilk test showed that most of the variables had a normal distribution. Although not all the variables fulfilled normality, we opted for a parametric analysis based on the following factors: 1) the Q-Q plot showed a linear relationship; 2) all variables showed homogeneity of variances according to Levene's test; 3) the parametric analysis showed practically identical results to those of the nonparametric analysis, the results obtained with the parametric analysis being more conservative; and 4) parametric tests have greater power and allow a better interpretation of the results.

The continuous variables were presented as mean ± standard deviation (SD), whereas the categorical variables were presented as absolute values. A one-way ANOVA was used to detect differences between groups in the anthropometric data and in the confounding variables (catastrophizing, kinesiophobia, anxiety, and depression). For the sex variable, the differences between groups were evaluated by the chi-squared test. In addition, the group x side interaction was evaluated for PPTs, observing an absence of differences for the side factor in all groups. However, we only unified the values obtained in the tibia because we considered it important not to merge the data of the upper limb, where the different interventions were applied, with those of the contralateral limb. Hence, the PPT variable for the tibia was created using an average.

Repeated measures ANOVA models were used to analyse the data of the PPT, the hypothesis of interest being the interaction group x time. Indeed, time (pre and post-intervention), group (SW-DP, SW-MP, and CPT), and time x group interaction analyses were carried out for PPT assessments. The effect size of the repeated measures ANOVA was calculated according to the coefficient of the partial eta-squared ($\eta^2 p$), which allowed classifying the effect size as small (0.01–0.059), medium (0.06–0.139), or large (> 0.14).[47] Multiple comparisons between groups (SW-DP, SW-MP, and CPT) were performed for the intergroup difference of means of change between groups by applying the Bonferroni correction. Cohen's *d* was used as a measure of the effect size for multiple comparison tests, considering small values ranging from 0.2–0.49, moderate values ranging from 0.5–0.79, and large values greater than or equal to 0.8.[48] All statistical tests were interpreted using a significance level of 5%.

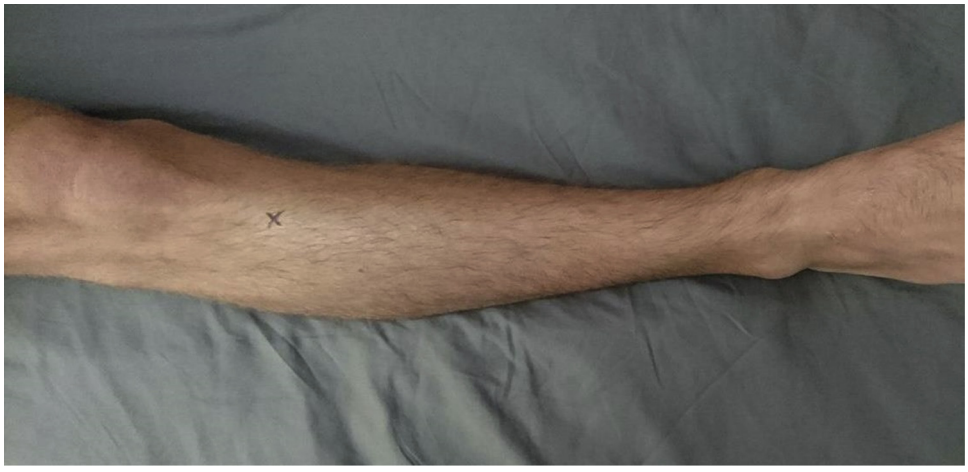

Fig. 3. Point in the muscular belly of the tibialis anterior.

Table 1
Clinical and anthropometric variables between both groups.

	SW-DP	SW-MP	CPT	P value
N	22	21	20	
Age (years)	22.64 ± 1.89	22.81 ± 1.6	23.45 ± 3.17	0.493*
Women:men	10:12	13:8	10:10	0,540†
Height (cm)	170.5 ± 7.76	173 ± 8.07	171.6 ± 11.2	0.657*
Weight (kg)	62.05 ± 11.98	65.86 ± 12.3	67.2 ± 13.11	0.381*
Kinesiofobia	18.36 ± 3.66	17.05 ± 4.18	18.75 ± 4.34	0.372*
Catastrophism	3.86 ± 3.29	3.52 ± 5.43	4.95 ± 5.46	0.615*
HADS-Anxiety	2.77 ± 2.02	3.43 ± 1.66	3.90 ± 1.86	0.150*
HADS-Depression	1.14 ± 1.46	1.48 ± 1.29	2.15 ± 2.18	0.149*

Abbreviations: SW-DP shock waves with mild pain; SW-MP shock waves with moderate pain; CPT cold pressor test; HADS Hospital Anxiety and Depression Scale.

* Variance analysis (ANOVA) for independent samples.

† Chi-Square test.

3. Results

3.1. Participants

The final sample consisted of 63 asymptomatic participants with a mean age of 22.95 ± 2.29 years, of whom 53% were women. There were no dropouts or losses during the study, nor any adverse effects during the interventions. All the participants received an average energy intensity of 0.08 mJ/mm^2 to 0.28 mJ/mm^2 (1.87–4 bar), and none reached a high-energy intensity during the application of the technique (0.28 mJ/mm^2 to 0.6 mJ/mm^2). Furthermore, previous experience with SW therapy clinically was considered an exclusion criterion. In addition, the three groups were homogeneous, therefore comparable; as demonstrated by the absence of differences between groups for the anthropometric and psychological variables (confounding variables) at the beginning of the study. Table 1 shows the values obtained for the anthropometric and psychological variables belonging to each of the groups.

3.2. Outcome measurements

The results of the ANOVA revealed differences between the various groups in time for the totality of the PPT, due to statistically significant differences were obtained in the interaction group x time (lateral epicondyle dominant arm [F = 10.29; $P < 0.001$; $\eta^2p = 0.255$]; median nerve dominant arm [F = 8.05, $P = 0.001$, $\eta^2p = 0.212$]; lateral epicondyle non-dominant arm [F = 11.37, $P < 0.001$, $\eta^2p = 0.275$]; median nerve, non-dominant arm [F = 10.96, $P < 0.001$, $\eta^2p = 0.268$]; tibia [F = 4.80, $P = 0.012$, $\eta^2p = 0.138$]).

The results of the comparisons between groups are shown in Table 2. The PPTs increased significantly more in the SW-MP group compared with the SW-DP group. In addition, this increase showed a large effect size due to the obtained effect sizes were greater than 0.80.

However, the CPT group showed a significantly PPT increase with a high effect size ($d > 0.80$) with respect to the SW-DP group in the upper limb where the interventions were applied (dominant arm). In addition, there were no significant differences between the SW-MP group versus the CPT group except for the PPT obtained in the arm contralateral to the administration of the technique (nondominant upper limb), with differences observed in the latter of a moderate-large effect size ($d \geq 0.73$) in favour of the SW-MP group.

Regarding the intra-group changes, the two groups that reached moderate pain during the intervention showed significant differences in all the PPTs evaluated.

4. Discussion

The present study provides additional evidence on the possible mechanisms underlying the hypoalgesic effect attributed to SWs. Based on our results, only those interventions administered with moderate pain (SW-MP and CPT) caused an increase in the PPT in regions neurophysiologically related to the area of application, although the SW-MP group obtained superior results — especially in the arm contralateral to the administration of the technique. Hence, the hypothesis that the hypoalgesic effect of SW could be due to an activation of the descending inhibitory system.

In a review of the literature, there were numerous studies demonstrating a hypoalgesic effect through the application of SWs.[20,49–52] However, to our knowledge, there is no substantial evidence to determine the possible mechanisms responsible for this effect, as well as whether the perception of pain during the administration of the technique is a factor to be taken into account. Concerning our primary objective, the findings of the present investigation suggest that the hypoalgesic effect, generated from SWs, is linked to the magnitude of pain intensity perceived during its application, given that only the SW-MP group obtained an increase in PPT. This finding could be due to the activation of the descending inhibitory system because this system may be activated by the application of a considerable painful stimulus, resulting in a blockage or a reduction in the transmission of nociceptive information by the C fibres.[53]

On the other hand, our SWs application was always placed on medium energy parameters according to the Rompe rating scale,[33] as with the majority of studies performed on tendinopathies in which low or medium intensities are applied.[54] Some authors have investigated the role of energy intensity applied using SWs on the analgesic effect because the intensity of the energy flow is one of the most important parameters for the treatment of musculoskeletal disorders. In this way, Yang et al.[52] demonstrated that applying SWs with a high-energy intensity generated a greater analgesic effect —reduced pain intensity and increased PPT— than its application with an average intensity in patients with pain syndrome. However, for patients with calcific tendinopathy, Bannuru et al.[55] did not find differences in pain relief between the applications of SWs with high or low intensity of energy — although there was a tendency towards a more significant effect with high intensity — but in the improvement of function. In our opinion, this aspect could have some relationship to our findings, given that usually, the more energy that is applied during the technique, the greater is the discomfort or the perception of pain. Therefore, it could be hypothesised that the greater pain relief produced by the application of SWs with high-intensity energy may be due to the greater perception of pain/discomfort during its administration, and not to the intensity of energy applied in itself. This hypothesis could explain the ambiguity of results observed in the literature on the appropriate intensity/effectiveness of SWs since the endogenous analgesic effect depends to a greater extent on the characteristics of each individual than on the nociceptive stimulus.[56]

At present, the mechanisms responsible for the analgesic effect of SWs are unknown. The present study, although it does not adequately clarify those mechanisms, contributes to its understanding. When comparing the effect of SWs with the CPT, the theory that the hypoalgesic effect is based on the activation of the descending inhibitory system seems more relevant because only groups with moderate pain generated hypoalgesic changes. However, in the presence of a painful stimulus of the same intensity, the hypoalgesia by the pressure obtained with the SWs was higher and more generalised than the hypoalgesia by the CPT. This finding could be argued because SWs repeatedly reached the pre-established pain intensity in multiple participants due to the application of 2000 impulses because a maximum of two pauses could be made, whereas the only one was made with the CPT. Therefore, it would be expected that the repeated summation in time of moderate stimuli would suppose a greater endogenous analgesic activation, thus elevating the PPT in a generalised manner. Another hypothesis to justify the superiority of the SW-MP group compared with the CPT is the latter uses thermal rather than mechanical stimuli to induce analgesia,

Table 2
Comparison of pain threshold to pressure before and after treatment with shock waves and with the cold pressor test.

Variable	Group	Mean ± standard deviation		Intragroup difference of means (CI at 95%); effect size (d)	Intergroup difference of means of change between groups (CI at 95%); effect size (d) a) SW-DP vs SW-MP b) SW-DP vs CPT c) SW-MP vs CPT
		Pre	Post		
PTP-D-Epi	SW-DP	4.32 (1.54)	4.55 (1.48)	−0.23 (−0.63 to 0.16); d = −0.15	a) 1.25 (0.56–1.94)**; d = 1.47
	SW-MP	5.06 (1.72)	6.54 (2.19)	−1.48 (−1.88 to −1.08)**; d = −0.75	b) 0.82 (0.13–1.52)*; d = 0.99
	CPT	4.86 (1.16)	5.91 (1.59)	−1.06 (−1.47 to −0.65)**; d = −0.75	c) −0.42 (−1.13 to 0.28); d = −0.39
PTP-NoD-Epi	SW-DP	4.48 (1.65)	4.63 (1.63)	−0.15 (−0.50 to 0.19); d = −0.09	a) 1.18 (0.57–1.78)**; d = 1.37
	SW-MP	4.97 (1.79)	6.29 (2.35)	−1.33 (−1.68 to −0.97)**; d = −0.63	b) 0.53 (−0.08 to 1.15); d = 0.79
	CPT	4.83 (1.31)	5.52 (1.48)	−0.69 (−1.05 to −0.32)**; d = −0.49	c) −0.64 (−1.26 to −0.02)*; d = −0.73
PTP-D-Med	SW-DP	4.09 (1.97)	4.31 (1.78)	−0.23 (−0.60 to 0.15); d = −0.12	a) 0.87 (0.21–1.53)**; d = 0.97
	SW-MP	5.25 (1.76)	6.35 (2.18)	−1.1 (−1.48 to −0.72)**; d = −0.56	b) 0.98 (0.32–1.65)**; d = 1.23
	CPT	4.33 (0.96)	5.53 (1.22)	−1.21 (−1.61 to −0.82)**; d = −1.09	c) 0.11 (−0.57 to 0.79); d = 0.12
PTP-NoD-Med	SW-DP	3.82 (1.69)	4 (1.76)	−0.19 (−0.46 to 0.09); d = −0.10	a) 0.93 (0.44–1.42)**; d = 1.51
	SW-MP	4.43 (1.39)	5.55 (1.7)	−1.12 (−1.40 to −0.83)**; d = −0.72	b) 0.39 (−0.11 to 0.89); d = 0.60
	CPT	4.12 (0.87)	4.69 (1.11)	−0.57 (−0.87 to −0.28)**; d = −0.57	c) −0.54 (−1.05 to −0.09)*; d = −0.76
PTP-D-Tib and NoD	SW-DP	8.34 (3.16)	8.71 (3.06)	−0.37 (−0.75 to 0.02); d = −0.12	a) 0.86 (0.18–1.54)*; d = 0.88
	SW-MP	9.84 (2.36)	11.07 (2.5)	−1.22 (−1.62 to −0.83)**; d = −0.51	b) 0.43 (−0.26 to 1.12); d = 0.58
	CPT	9.07 (2.32)	9.87 (2.16)	−0.80 (−1.21 to −0.39)**; d = −0.36	c) −0.43 (−1.12 to 0.27); d = −0.42

Abbreviations: CI, confidence interval; PTP-D-Epipain threshold to pressure in the dominant epicondyle; PTP-NoD-Epi: pain threshold to pressure in the non-dominant epicondyle; PTP-D-Med: pain threshold to pressure in the dominant median nerve; PTP-NoD-Med: pain threshold to pressure in the non-dominant median nerve; PTP-D-Tib and NoD, mean of the pain threshold to the pressure in the dominant and non-dominant anterior tibial. SW-MP shock waves with moderate pain; SW-DP shock waves with mild pain; CPTcold pressor test.

* Statistically significant differences at $P < 0.05$.

** Statistically significant differences at $P < 0.01$.

which could have some repercussions due to the hypoalgesia was evaluated mechanically. The fibres responsible for the transmission of nociceptive information from mechanical stimuli to pressure are different from those responsible when the stimulus is cold;[57] thus, the results could have varied if the hypoalgesic effect had been evaluated as thermal pain thresholds. However, we used the CPT and not a conditioning stimulus of a mechanical nature, such as the tourniquet test,[58] because CPT application time is more similar to that used for SWs. Future studies should evaluate whether the modulation of pain conditioned by thermal stimuli differs from that obtained by mechanical stimuli. Finally, participants were not possibly influenced by the expectations for SWs and CPT interventions, due to participants with prior experiences under these interventions were excluded.[59] Thus, this aspect could influence the magnitude of the hypoalgesic effect obtained by the CPT compared with the application of SWs.

Finally, the absence of hypoalgesic effect observed in the SW-DP group could suggest that the descending inhibitory system needs a stimulus of higher intensity than that caused in the SW-DP group to activate and generate significant changes. In our opinion, these findings are especially relevant in the clinical setting because they suggest that the hypoalgesic effect of SWs could underlie the perception of pain during its application rather than a therapeutic effect itself. This would imply that other types of interventions, such as therapeutic exercise, could possibly be more appropriate for the treatment of tendinopathies. However, these statements must be interpreted with caution considering that the results of the SW-MP group were superior to those of the CPT. Furthermore, it is possible that the hypoalgesic effects of SWs are due to histological tissue changes; thus, the present study cannot adequately establish that the produced hypoalgesia is entirely due to the activation of the descending inhibitory system. In addition, more significant shear forces seem to occur if energy levels are increased, although there is a lack of knowledge about the effects comparison between painful and non-painful SWs as well as their potential mechanical modulation which could be partially explained by the gate control theory of pain.[60]

4.1. Futures studies and clinical implications

Specific future studies about the application of SWs causing mild pain, SWs generating moderate pain and CPT should be carried out in patients with musculoskeletal conditions and compared to placebo, intervention absence or non-painful SW, due to different pain modulation mechanisms may be presented under different musculoskeletal conditions such as myofascial pain or fibromyalgia.[61–63]

In addition, prior studies have tested the descending inhibitory system activation by means of conditioned pain modulation or diffuse noxious inhibitory controls.[64–67] We suggest that the degree of inhibition by SW-MP and CPT should be equal in order to hypothesize the activation of the descending inhibitory system, but one of the biggest challenges in this field is the weak consistency across these studies.[64–68] In the same line, we supposed the link between painful and non-painful SW differences to activation of the descending inhibitory system. This system may contribute to the observed differences. Nevertheless, the descending inhibitory system acts best contralaterally and on C-fibers, and consequently the painful conditioning stimulus should be given to a different segment in order to exclude segmental inhibitory mechanisms.[64–67]

4.2. Limitations

This study has several limitations. First, the studied population was asymptomatic, therefore, the findings cannot be extrapolated to the pathological population. Due to we could not evaluate changes in the pain intensity and the state of the tissues, it is impossible to determine with certainty the SWs' mechanisms of action. All participants achieved a pain intensity of 6/10 on the VAS with the CPT, some participants even before 2 min. As the VAS scores was continuously evaluated, these values were not recorded. Nevertheless, all participants reached the pain intensity corresponding to their group, which was considered the most relevant aspect. In addition, only the immediate differences in the PPT were evaluated; future studies should assess the hypoalgesic effects covering more somatosensory variables and with a longer follow-up period. Finally, sex differences both in pain perception and pain

modulation may influence the PPT results, due to women generally exhibit greater pain sensitivity, enhanced pain facilitation and reduced pain inhibition compared with men.[69] Ideally, future studies should be designed with the additional aim to detect sex differences.

5. Conclusion

The results show that SWs treatment only has hypoalgesic effects if its application produces moderate pain. In addition, the SW-MP group showed a greater hypoalgesic effect in the contralateral limb of application than the CPT group. Finally, the CPT group obtained local hypoalgesic changes concerning the SW-MP group. These findings suggest that the hypoalgesic effect obtained after the application of SW could be partially explained by the activation of the descending inhibitory system. However, the results of this study should be interpreted with caution due to it was performed on asymptomatic participants and further studies testing conditioned pain modulation or diffuse noxious inhibitory controls should be carried out in order to link these hypoalgesic changes to the activation of the descending inhibitory systems.

Conflicts of interest

No conflicts of interest.

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References

1. Seil R, Wilmes P, Nührenbörger C. Extracorporeal shock wave therapy for tendinopathies. *Expert Rev Med Dev.* 2006;3(4):463–470. https://doi.org/10.1586/17434440.3.4.463.
2. van der Worp H, van den Akker-Scheek I, van Schie H, et al. ESWT for tendinopathy: technology and clinical implications. *Knee Surg Sports Traumatol Arthrosc.* 2013;21(6):1451–1458. https://doi.org/10.1007/s00167-012-2009-3.
3. Chang K-V, Chen S-Y, Chen W-S, Tu Y-K, Chien K-L. Comparative effectiveness of focused shock wave therapy of different intensity levels and radial shock wave therapy for treating plantar fasciitis: a systematic review and network meta-analysis. *Arch Phys Med Rehabil.* 2012;93(7):1259–1268. https://doi.org/10.1016/j.apmr.2012.02.023.
4. Storheim K, Gjersing L, Bølstad K, Risberg M. Extracorporeal shock wave therapy (ESWT) and radial extracorporeal shock wave therapy (rESWT) in chronic musculoskeletal pain. *Tidsskr Den Nor legeforening.* 2010;130(23):2360–2364. https://doi.org/10.4045/tidsskr.09.0654.
5. van der Worp H, Zwerver J, Hamstra M, et al. No difference in effectiveness between focused and radial shockwave therapy for treating patellar tendinopathy: a randomized controlled trial. *Knee Surg Sports Traumatol Arthrosc.* 2014;22(9):2026–2032. https://doi.org/10.1007/s00167-013-2522-z.
6. Król P, Franek A, Durmała J, et al. Focused and Radial shock wave therapy in the treatment of tennis elbow: a pilot randomised controlled study. *J Hum Kinet.* 2015;47(1):127–135. https://doi.org/10.1515/hukin-2015-0068.
7. Yang T-H, Huang Y-C, Lau Y-C, Wang L-Y. Efficacy of radial extracorporeal shock wave therapy on lateral epicondylosis, and changes in the common extensor tendon stiffness with pretherapy and posttherapy in real-time sonoelastography. *Am J Phys Med Rehabil.* 2017;96(2):93–100. https://doi.org/10.1097/PHM.0000000000000547.
8. Ilieva EM, Minchev RM, Petrova NS. Radial shock wave therapy in patients with lateral epicondylitis. *Folia Med (Plovdiv).* 2012;54(3):35–41.
9. Andres BM, Murrell GAC. Treatment of tendinopathy: what works, what does not, and what is on the horizon. *Clin Orthop Relat Res.* 2008;466(7):1539–1554. https://doi.org/10.1007/s11999-008-0260-1.
10. Childress MA, Beutler A. Management of chronic tendon injuries. *Am Fam Phys.* 2013;87(7):486–490.
11. Al-Abbad H, Simon JV. The effectiveness of extracorporeal shock wave therapy on chronic achilles tendinopathy. *Foot Ankle Int.* 2013;34(1):33–41. https://doi.org/10.1177/1071100712464354.
12. Ho C. Extracorporeal shock wave treatment for chronic lateral epicondylitis (tennis elbow). *Issues Emerg Health Technol.* 2007;96(Part 2):1–4.
13. Radwan YA, ElSobhi G, Badawy WS, Reda A, Khalid S. Resistant tennis elbow: shock-wave therapy versus percutaneous tenotomy. *Int Orthop.* 2008;32(5):671–677. https://doi.org/10.1007/s00264-007-0379-9.
14. Notarnicola A, Moretti B. The biological effects of extracorporeal shock wave therapy (eswt) on tendon tissue. *Muscles Ligaments Tendons J.* 2012;2(1):33–37.
15. Schmitz C, Császár NBM, Milz S, et al. Efficacy and safety of extracorporeal shock wave therapy for orthopedic conditions: a systematic review on studies listed in the PEDro database. *Br Med Bull.* 2015;116:115–138. https://doi.org/10.1093/bmb/ldv047.
16. Wang C-J. Extracorporeal shockwave therapy in musculoskeletal disorders. *J Orthop Surg Res.* 2012;7:11. https://doi.org/10.1186/1749-799X-7-11.
17. Ogden JA, Tóth-Kischkat A, Schultheiss R. Principles of shock wave therapy. *Clin Orthop Relat Res.* 2001(387):8–17.
18. d'Agostino MC, Craig K, Tibalt E, Respizzi S. Shock wave as biological therapeutic tool: From mechanical stimulation to recovery and healing, through mechanotransduction. *Int J Surg.* 2015;24(Pt B):147–153. https://doi.org/10.1016/j.ijsu.2015.11.030.
19. Saggini R, Di Stefano A, Saggini A, Bellomo RG. Clinical application of shock wave therapy in musculoskeletal disorders: Part I. *J Biol Regul Homeost Agents.* 2015;29(3):533–545.
20. Cho Y-S, Park S-J, Jang S-H, Choi Y-C, Lee J-H, Kim J-S. Effects of the Combined Treatment of Extracorporeal Shock Wave Therapy (ESWT) and stabilization exercises on pain and functions of patients with myofascial pain syndrome. *J Phys Ther Sci.* 2012;24:1319–1323.
21. Ji HM, Kim HJ, Han SJ. Extracorporeal shock wave therapy in myofascial pain syndrome of upper trapezius. *Ann Rehabil Med.* 2012;36(5):675–680. https://doi.org/10.5535/arm.2012.36.5.675.
22. Beyazal MS, Devrimsel G. Comparison of the effectiveness of local corticosteroid injection and extracorporeal shock wave therapy in patients with lateral epicondylitis. *J Phys Ther Sci.* 2015;27(12):3755–3758. https://doi.org/10.1589/jpts.27.3755.
23. Yarnitsky D. Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): Its relevance for acute and chronic pain states. *Curr Opin Anaesthesiol.* 2010;23(5):611–615. https://doi.org/10.1097/ACO.0b013e32833c348b.
24. Xia W, Mørch CD, Matre D, Andersen OK. Exploration of conditioned pain modulation effect on long-term potentiation-like pain amplification in humans. *Eur J Pain.* 2017;21(4):645–657. https://doi.org/10.1002/ejp.968.
25. Chow IHW, Cheing GL. Comparison of different energy densities of extracorporeal shock wave therapy (ESWT) for the management of chronic heel pain. *Clin Rehabil.* 2007;21(2):131–141. https://doi.org/10.1177/0269215506069244.
26. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med.* 2010;152(11):726–732. https://doi.org/10.7326/0003-4819-152-11-201006010-00232.
27. Steinbach P, Hofstaedter F, Nicolai H, Roessler W, Wieland W. Determination of the energy-dependent extent of vascular damage caused by high-energy shock waves in an umbilical cord model. *Urol Res.* 1993;21(4):279–282.
28. Steinbach P, Hofstädter F, Nicolai H, Rössler W, Wieland W. In vitro investigations on cellular damage induced by high energy shock waves. *Ultrasound Med Biol.* 1992;18(8):691–699.
29. Zhang X, Yan X, Wang C, Tang T, Chai Y. The dose-effect relationship in extracorporeal shock wave therapy: the optimal parameter for extracorporeal shock wave therapy. *J Surg Res.* 2014;186(1):484–492. https://doi.org/10.1016/j.jss.2013.08.013.
30. Toro JR, Rebollo AG. Tratamiento de las epicondilitis crónica con ondas de choque. *Rehabilitación.* 2004;38(4):175–181.
31. Lohrer H, Nauck T, Korakakis V, Malliaropoulos N. Historical ESWT paradigms are overcome: a narrative review. *Biomed Res Int.* 2016;2016:3850461. https://doi.org/10.1155/2016/3850461.
32. Schmitz C, Császár NBM, Milz S, et al. Efficacy and safety of extracorporeal shock wave therapy for orthopedic conditions: a systematic review on studies listed in the PEDro database. *Br Med Bull.* 2015;116:ldv047. https://doi.org/10.1093/bmb/ldv047.
33. Rompe JD, Kirkpatrick CJ, Küllmer K, Schwitalle M, Krischek O. Dose-related effects of shock waves on rabbit tendo Achillis. A sonographic and histological study. *J Bone Joint Surg Br.* 1998;80(3):546–552.
34. Lewis GN, Rice DA, McNair PJ. Conditioned pain modulation in populations with chronic pain: a systematic review and meta-analysis. *J Pain.* 2012;13(10):936–944. https://doi.org/10.1016/j.jpain.2012.07.005.
35. Myburgh C, Lauridsen HH, Larsen AH, Hartvigsen J. Standardized manual palpation of myofascial trigger points in relation to neck/shoulder pain; the influence of clinical experience on inter-examiner reproducibility. *Man Ther.* 2011;16(2):136–140. https://doi.org/10.1016/j.math.2010.08.002.
36. Morales MA, Lorenzo CM. Dolor y estrés en fisioterapia: algometría de presión Pain and stress. *Pain.* 2006;9(1):3–10. https://doi.org/10.1016/S1138-6045(06)73109-4.
37. Fryer G, Hodgson L. The effect of manual pressure release on myofascial trigger points in the upper trapezius muscle. *J Bodyw Mov Ther.* 2005;9(4):248–255. https://doi.org/10.1016/j.jbmt.2005.02.002.
38. Zuil Escobar JC, García M, Pozo D, González Propin M. Modificaciones del umbral de dolor en un punto gatillo miofascial tras técnica de energía muscular. *Rev la Soc Esp Dolor.* 2010;17:313–319. https://doi.org/10.1016/j.resed.2010.09.003.
39. Koo TK, Guo J, Brown CM. Test-retest reliability, repeatability, and sensitivity of an automated deformation-controlled indentation on pressure pain threshold measurement. *J Manipulative Physiol Ther.* 2013;36(2):84–90. https://doi.org/10.1016/j.jmpt.2013.01.001.
40. Brellenthin AG, Crombie KM, Cook DB, Sehgal N, Koltyn KF. Psychosocial influences on exercise-induced hypoalgesia. *Pain Med.* 2016;18(3):pnw275. https://doi.org/10.1093/pm/pnw275.
41. Walton DM, Levesque L, Payne M, Schick J. Clinical pressure pain threshold testing in neck pain: comparing protocols, responsiveness, and association with psychological variables. *Phys Ther.* 2014;94(6):827–837. https://doi.org/10.2522/ptj.20130369.
42. Gómez-Pérez L, López-Martínez AE, Ruiz-Párraga GT. Psychometric properties of the Spanish version of the tampa scale for kinesiophobia (TSK). *J Pain.*

2011;12(4):425–435. https://doi.org/10.1016/j.jpain.2010.08.004.
43. García Campayo J, Rodero B, Alda M, et al. Validation of the Spanish version of the pain catastrophizing scale in fibromyalgia. *Med Clin (Barc).* 2008;131(13):487–492.
44. Herrero MJ, Blanch J, Peri JM, De Pablo J, Pintor L, Bulbena A. A validation study of the hospital anxiety and depression scale (HADS) in a Spanish population. *Gen Hosp Psychiatry.* 2003;25(4):277–283. https://doi.org/10.1016/S0163-8343(03)00043-4.
45. Ahlers SJGM, van der Veen AM, van Dijk M, et al. The use of the behavioral pain scale to assess pain in conscious sedated patients. *Anesth Analg.* 2010;110(1):127–133. https://doi.org/10.1213/ANE.0b013e3181c3119e.
46. Bijur PE, Silver W, Gallagher EJ. Reliability of the visual analog scale for measurement of acute pain. *Acad Emerg Med.* 2001;8(12):1153–1157.
47. Cohen J. Eta-squared and partial eta-squared in fixed factor ANOVA designs. *Educ Psychol Meas.* 1973;33:107–112.
48. Cohen J. Statistical power analysis for the behavioral sciences. *Stat Power Anal Behav Sci.* 1988:567. https://doi.org/10.1234/12345678 2nd.
49. Ali SA, Lasheen YR, Kamel RM, Genaidy AF. Efficacy of shockwave therapy in treatment of myofascial trigger points of rotator cuff muscle dysfunction. *Int J Pharm Tech Res.* 2016;9(6):115–126.
50. Jeon JH, Jung YJ, Lee JY, et al. The effect of extracorporeal shock wave therapy on myofascial pain syndrome. *Ann Rehabil Med.* 2012;36(5):665–674. https://doi.org/10.5535/arm.2012.36.5.665.
51. Jung YJ, Park WY, Jeon JH, et al. Outcomes of ultrasound-guided extracorporeal shock wave therapy for painful stump neuroma. *Ann Rehabil Med.* 2014;38(4):523–533. https://doi.org/10.5535/arm.2014.38.4.523.
52. Yang Y-J, Lee S-J, Choi M. Pressure pain threshold and visual analogue scale changes in the high and low energy extracorporeal shock wave. *Phys Ther Rehabil Sci.* 2014;3(2):142–147. https://doi.org/10.14474/ptrs.2014.3.2.142.
53. Ossipov MH, Dussor GO, Porreca F. Central modulation of pain. *J Clin Invest.* 2010;120(11):3779–3787. https://doi.org/10.1172/JCI43766.
54. Sems A, Dimeff R, Iannotti JP. Extracorporeal shock wave therapy in the treatment of chronic tendinopathies. *J Am Acad Orthop Surg.* 2006;14(4):195–204.
55. Bannuru RR, Flavin NE, Vaysbrot E, Harvey W, McAlindon T. High-energy extracorporeal shock-wave therapy for treating chronic calcific tendinitis of the shoulder. *Ann Intern Med.* 2014;160(8):542. https://doi.org/10.7326/M13-1982.
56. Granot M, Weissman-Fogel I, Crispel Y, et al. Determinants of endogenous analgesia magnitude in a diffuse noxious inhibitory control (DNIC) paradigm: do conditioning stimulus painfulness, gender and personality variables matter? *Pain.* 2008;136(1):142–149. https://doi.org/10.1016/j.pain.2007.06.029.
57. Perena M, Perena M, Romera E. V I S I Ó N RE, rena PM, -ra Neuroanatomy RE. Neuroanatomía del dolor. *Rev Soc Esp Dolor Supl II.* 2000;7:5–10.
58. Lindstedt F, Berrebi J, Greayer E, et al. Conditioned pain modulation is associated with common polymorphisms in the serotonin transporter gene. *PLoS One.* 2011;6(3):e18252. https://doi.org/10.1371/journal.pone.0018252.
59. Beasley MJ, Ferguson-Jones EA, Macfarlane GJ. Treatment expectations but not preference affect outcome in a trial of CBT and exercise for pain. *Can J Pain.* 2017;1(1):161–170. https://doi.org/10.1080/24740527.2017.1384297.
60. Mendell LM. Constructing and deconstructing the gate theory of pain. *Pain.* 2014;155(2):210–216. https://doi.org/10.1016/j.pain.2013.12.010.
61. Kim Y, Kim J, Shim JK, Suh D-W, Yoon B. The hypoalgesic effect of remote tactile sensory modulation on the mechanical sensitivity of trigger points: A randomized controlled study. *NeuroRehabilitation.* 2014;35(3):607–614. https://doi.org/10.3233/NRE-141156.
62. Price DD, Staud R, Robinson ME, Mauderli AP, Cannon R, Vierck CJ. Enhanced temporal summation of second pain and its central modulation in fibromyalgia patients. *Pain.* 2002;99(1–2):49–59 Accessed 26 November 2018 http://www.ncbi.nlm.nih.gov/pubmed/12237183.
63. Moont R, Crispel Y, Lev R, Pud D, Yarnitsky D. Temporal changes in cortical activation during conditioned pain modulation (CPM), a LORETA study. *Pain.* 2011;152(7):1469–1477. https://doi.org/10.1016/j.pain.2011.01.036.
64. Treister R, Eisenberg E, Gershon E, Haddad M, Pud D. Factors affecting - and relationships between-different modes of endogenous pain modulation in healthy volunteers. *Eur J Pain.* 2010;14(6):608–614. https://doi.org/10.1016/j.ejpain.2009.10.005.
65. Pud D, Golan Y, Pesta R. Hand dominancy—a feature affecting sensitivity to pain. *Neurosci Lett.* 2009;467(3):237–240. https://doi.org/10.1016/j.neulet.2009.10.048.
66. Nahman-Averbuch H, Granovsky Y, Coghill RC, Yarnitsky D, Sprecher E, Weissman-Fogel I. Waning of "Conditioned Pain Modulation": a novel expression of subtle pronociception in migraine. *Headache J Head Face Pain.* 2013;53(7):1104–1115. https://doi.org/10.1111/head.12117.
67. Moont R, Crispel Y, Lev R, Pud D, Yarnitsky D. Temporal changes in cortical activation during distraction from pain: a comparative LORETA study with conditioned pain modulation. *Brain Res.* 2012;1435:105–117. https://doi.org/10.1016/j.brainres.2011.11.056.
68. Moont R, Pud D, Sprecher E, Sharvit G, Yarnitsky D. 'Pain inhibits pain' mechanisms: is pain modulation simply due to distraction? *Pain.* 2010;150(1):113–120. https://doi.org/10.1016/j.pain.2010.04.009.
69. Bartley EJ, Fillingim RB. Sex differences in pain: a brief review of clinical and experimental findings. *Br J Anaesth.* 2013;111(1):52–58. https://doi.org/10.1093/bja/aet127.