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ORIGINAL ARTICLE

Synergic effects of ultrasound and laser on the pain relief in women with hand osteoarthritis

Alessandra Rossi Paolillo · Fernanda Rossi Paolillo · Jessica Patrícia João · Herbert Alexandre João · Vanderlei Salvador Bagnato

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Abstract Patients with pain avoid movements, leading to a gradual impairment of their physical condition and functionality. In this context, the use of ultrasound (US) and low-level laser therapy (LLLT) show promising results for nonpharmacological and noninvasive treatment. The aim of this study was evaluated the synergistic effects of the US and the LLLT (new prototype) with or without therapeutic exercises (TE) on pain and grip strength in women with hand osteoarthritis. Forty-five women with hand osteoarthritis, aged 60 to 80 years, were randomly assigned to one of three groups, but 43 women successfully completed the full study. The three groups were as follows: (i) the placebo group which did not perform TE, but the prototype without emitting electromagnetic or mechanical waves was applied (n=11); (ii) the US + LLLT group which carried out only the prototype (n=13); and (iii) the TE + US + LLLT group which performed TE before the prototype is applied (n=13). The parameters of US were frequency 1 MHz; 1.0 W/cm^2 intensity, pulsed mode 1:1 (duty cycle 50 %). Regarding laser, the output power of the each laser was fixed at 100 mW leading to an energy value of 18 J per laser. Five points were irradiated per hand, during 3 min per point and 15 min per session. The prototype was applied after therapeutic exercises. The treatments are done once a week for 3 months. Grip strength and pressure pain thresholds (PPT) were measured. Grip strength did not differ significantly for any of the groups ($p \geq 0.05$). The average PPT between baseline and 3 months shows significant decrease of the pain sensitivity for both the US + LLLT group (Δ=30±19 N, p 0.001) and the TE + US + LLLT group (Δ=32±13 N, $p<0.001$). However, there were no significant differences in average PPT for placebo group (Δ=−0.3±9 N). There was no placebo effect. The new prototype that combines US and LLLT reduced pain in women with hand osteoarthritis.

Keywords Ultrasound · Laser · Pain · Osteoarthritis · Hand · Women

A. R. Paolillo · F. R. Paolillo · J. P. João · H. A. João · V. S. Bagnato
Optics Group from Physics Institute of São Carlos (IFSC), University of São Paulo (USP), Av. Trabalhador Sãocarlense, 400-Centro, CEP 13560-970 São Carlos, SP, Brazil

F. R. Paolillo
e-mail: fer.nanda.rp@hotmail.com

J. P. João
e-mail: jessicapatriciaj@hotmail.com

H. A. João
e-mail: herbert@ifsc.usp.br

V. S. Bagnato
e-mail: vander@ifsc.usp.br

A. R. Paolillo (✉)
Department of Occupational Therapy, Federal University of São Carlos (UFSCar), Rodovia Washington Luiz, Km. 235, CEP 13565-905 São Carlos, SP, Brazil
e-mail: arpaolillo@gmail.com

Introduction

Osteoarthritis (OA) is the most common joint disorder and with fastest growing public health concern, reflecting the aging of the population [1]. The clinical symptoms and consequences of hand OA are, for example, pain, reduced joint range, and deformity with interference in grip and fine precision pinch, muscle weakness, and dissatisfaction with cosmetic appearance [2].

Patients with pain, especially chronic pain, avoid movements. This in turn results in a gradual impairment of their physical condition, reducing, for example, strength, flexibility, physical functionality, and occupational activity. All of the recent guidelines recommend therapeutic exercise for chronic, subacute, and postsurgical OA for improvement of physical functionality and life quality [2, 3]. Previous studies from our

group observed the potential effects of exercise associated with phototherapy to improve muscle function and health-related outcomes [4–7].

Low-level laser therapy (LLLT) is a form of phototherapy with application of low-power monochromatic or quasimonochromatic and coherent electromagnetic radiation in the therapeutic optical region of ~600–1,000 nm. The light is absorbed by mitochondria and alters cell metabolism without any thermal damage or destructive effects [8]. In parallel, ultrasound (US) is a source of mechanical wave. The energy is transmitted by the vibrations of molecules through the medium such as a solid, liquid, or gas with absorption of mechanical energy by body tissues. Then, the vibrational energy is converted into molecular energy with both thermal and cavitation effects [9].

There are several therapeutic effects of the US or LLLT, including pain relief, increase of microcirculation, enzymatic activity, and collagen synthesis, as well as a modulation of inflammatory response and accelerated tissue repair, e.g., skin, muscle, tendon, nerve, cartilage, and bone [10]. In this context, a combination of US, LLLT, and therapeutic exercise [11] may maximize clinical outcome.

Several studies investigated the effects of US [12, 13] or LLLT [14, 15] on pain relief, range of motion, and grip strength, but few clinical trials were performed with hands OA [16]. In addition, the effects of US together with LLLT for treatment of hand OA, to our knowledge, have not been investigated.

The aim of this study was evaluated the synergistic effects of the US and LLLT (prototype) with or without therapeutic exercises (TE) on grip strength and pain in women with hands OA. We hypothesized that the new prototype associated with TE may help relieve pain and improve grip strength.

Materials and methods

The current research has been approved by the National Ethics Committee of Ministry of Health in Brasilia, Brazil (approval no. 362.789) and by the Ethics Committee of Federal University of São Carlos (UFSCar) in São Carlos, Brazil (approval no. 143.392). The study was registered with NIH clinical trials (NCT02154893). All subjects signed written informed consents before their participation in the study.

This study was performed on 45 Caucasian women with hand osteoarthritis, aged between 60 and 80 years. Exclusion criteria were signs and symptoms of any psychiatric disorder, neurological, metabolic, pulmonary, cardiac disease, thrombosis, and/or cancer. We performed simple randomization by a computer program. Then, the subjects were randomly divided into three groups (15 per group), but 43 women successfully completed the full study: (i) the placebo group (n=11) which did not perform TE, but the device with US and LLLT without emitting electromagnetic or mechanical waves was applied (null dose); (ii) the US + LLLT group (n=13) which carried out only the prototype; and (iii) the TE + US + LLLT group (n=13) which performed TE before the prototype is applied.

Development of the prototype and clinical protocol

To perform physical treatments, a prototype device was developed by researchers of the Technological Support Laboratory (LAT) of the Optics Group from the Physics Institute of São Carlos (IFSC), University of São Paulo (USP), together with the company MM Optics Ltda. The device includes four diode laser beams (808 nm) around of the one US transducer (Fig. 1). The shape of each diode laser beam is elliptical, and four laser beams form a square around the transducer.

The output power of each laser was fixed at 100 mW [17, 18]. A FieldMaster TO-II optical power meter (Coherent Inc., Santa Clara, CA, USA) linked to a photodetector was used to calibrate this device and revaluated ~40 mW/cm^2 average optical power density. The treatment time was 3 min per point, leading to an energy value of 18 J and a fluence of 7 J/cm^2 per laser or 72 J and 28 J/cm^2 per point. Five points were irradiated per hand, leading to a total energy of 360 J and a fluence delivered close to 142 J/cm^2 per hand. The volunteers wore safety glasses.

The US includes 1–3 MHz frequency and 3.5 cm^2 effective radiation area (ERA). The parameters used were as follows: frequency 1 MHz, 1.0 W/cm^2 intensity, pulsed mode 1:1 (duty cycle 50 %), 0.5 W/cm^2 spatial average-temporal average (SATA) for 3 min per point, a total of five points per hand, and 15 min per hand per session, leading to 3.150 J total energy [12, 13, 19]. Transparent conductive gel was used. The interaction of transparent gel with radiation was investigated by the Cary-17 Spectrophotometer Conversion, OLIS (OnLine Instruments Systems Inc., Bogart, GA). The percent transmittance (% T) was defined as $100 \times I/I_0$, where I_0 is the intensity of light entering the sample, and I is the intensity of light leaving the sample. The results showed ~80 % of transmittance for the wavelengths between 600 and 1,000 nm. There was only small loss of intensity. It shows that the transparent gel does not appear to interfere negatively in treatment.

The prototype application techniques were identical for all groups, but the null dose was applied in the placebo group. The two hands were treated. The movements of the device were circular, continuous, slow, and smooth, contemplating all hand (left and right). The landmarks are not indicated by colored paint on the bare skin, because it can lead to loss of energy delivered from the laser to the skin. In addition, we do not use hand immersed in water or bladder application procedure, because these methods are appropriate for US; however, it also can lead to loss of laser energy. Then, we performed US

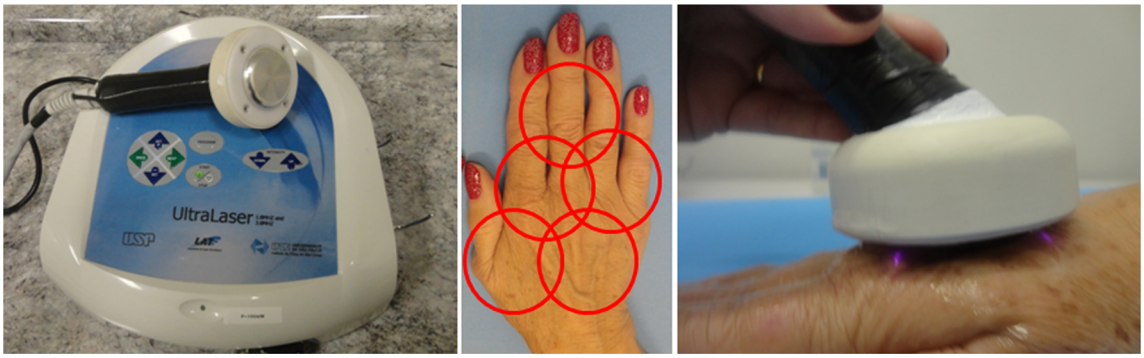

Fig. 1 Prototype with four diode laser beams around one US transducer, points of application on the hand, and US plus laser during therapeutic session

and LLLT for all hand with safety, mainly on bony protuberances and smaller muscles. The points of applications of the device on the hand are indicated in Fig. 1.

The prototype was applied after therapeutic exercises to prevent delayed onset muscle soreness (DOMS) or joint pain post-exercise in the TE + US + LLLT group. The therapeutic exercises consisted of two sensorimotor exercises with ball tennis, two stretching exercises for upper limb and resistance training using hand training device, DigiFlex® (IMC Products Corp., Hicksville, NY) [20], as seen in Fig. 2. The resistance levels 5, 10, 16, and 23 lbs per hand were used. The load was progressively increased over 2 months. Each load was maintained for 15 days. The patients performed ten grip movements at each session. After 2 months, the patients performed efforts (maximal number of grip movements) for 1 min per session with maximal load (23 lbs).

The prototype with or without therapeutic exercise was applied once a week for 3 months. Hand evaluations were performed on the baseline and after 3 months in a laboratory always at controlled air temperature (22–24 °C) and relative humidity (50–60 %).

Clinical characteristics

Clinical characteristics (Table 1) were measured as previously described [21]. Anthropometric data were used to determine the body mass index [BMI: body weight (in kg) divided by height (in m^2)] and the waist-to-hip ratio [WHR: waist circumference (in cm) divided by hip circumference (in cm)]. The body fat and hydration were measured by the bipolar electrical bioimpedance of the upper limbs (OMRON®, Kyoto, Japan).

Grip strength testing

Grip strength of the dominant limb was measured by the hand dynamometer (JAMAR Hydraulic Hand Dynamometer, Sammons Preston Inc, Bolingbrook, IL, USA) with patients sitting with the shoulder in a neutral position and the elbow flexed at 90°. The average force of three consecutive trials was calculated [22].

PPT measurement and topographical pressure pain sensitivity maps of the hand

A pressure pain threshold (PPT) is defined as the amount of pressure where a sense of pressure changes to pain. An electronic algometer (Wagner Instruments, Greenwich, CT, USA) was used to measure the PPT. The algometer consists of a 1 cm^2 rubber-tipped plunger mounted on a force transducer. The pressure was applied at a rate of approximately 1 $N/cm^2/s$ and the algometer scores are stated as newtons per square centimeter (N/cm^2) in all reported results [23]. The individual was instructed to ask to say "stop" when the sensation changed from pressure to pain. Thus, PPT represents the intensity at which a stimulus (amount of force or pressure) begins to evoke pain. Three PPT measurements (intraexaminer reliability) were taken at each point with a 20 s interval between two consecutive points to avoid effects of temporal summation [24].

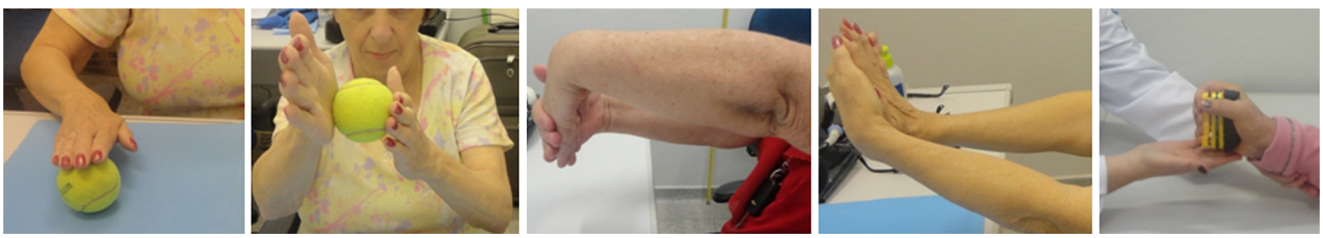

Fig. 2 Exercise protocol: sensorimotor exercises with ball tennis, stretching, and therapeutic exercise with DigiFlex®

Table 1 Clinical characteristics of the women with hand osteoarthritis

	Placebo group	US + LLLT group	TE + US + LLLT group
Age (years)	72±6	69±5	68±6
Body mass (kg)	70±16	68±11	76±14
Body height (m)	1.57±0.06	1.57±0.06	1.57±0.06
BMI (kg/m^2)	28±5	28±5	31±5
Waist (cm)	99±13	95±10	101±11
Hip (cm)	104±9	95±12	112±11
WHR	0.94±0.05	0.91±0.04	0.89±0.04
Fat (%)	38±9	41±9	43±9
Hydration (%)	43±6	39±8	39±6

No significant differences were found between the groups ($p \geq 0.05$)

The participants were instructed not to exercise on the previous day and not allowed to take analgesics or a muscle relaxant through the 72 h prior to the measurements. Subjects were asked to take a seated position, and PPT levels were measured at 30 locations on dominant hand as previously described [24]. The locations were as follows: distal phalanx (point 1), proximal phalanx (point 2), and thenar eminency (point 3); index finger—distal phalanx (point 4), middle phalanx (point 5), and proximal phalanx (point 6); middle finger—distal (point 7), middle (point 8), and proximal (point 9) phalanx; fourth finger—distal (point 10), middle (point 11), and proximal (point 12) phalanx; fifth finger—distal (point 13), middle (point 14), and proximal (point 15) phalanx; and head of the fifth (point 16), fourth (point 17), third (point 18), and second (point 19) metacarpal bones. For points 20–27, 2 cm equidistant points over each metacarpal bone were marked (20–24 over the second metacarpal bone, 21–25 over the third metacarpal bone, 22–26 over the fourth metacarpal bone, and 23–27 over the fifth metacarpal bone). Finally, one point over the lower end of the hypothenar eminency (point 28), over the carpal tunnel (point 29), and over the lower end of the thenar eminency (point 30) were also assessed.

Three measurements were performed at each location to obtain an average as previously described [24]. Averaged PPT values over the 30 locations were interpolated using an inverse distance weighted interpolation for the PPT distribution [24] over dominant hand of patients with OA. The Origin 8.0 software (OriginLab Corporation, Northampton, MA) was used to create the color schemes from average PPT values measured at 30 points on hand.

Statistical analysis

The Shapiro-Wilk test was used to analyze data normality and the homogeneity of variances using Levene's test. Two-way ANOVA with repeated measures was used to compare changes before and after the treatment. The independent factors were group (with three levels: TE + US + LLLT group, US + LLLT group, and Placebo group) and time (with two levels: pretreatment and posttreatment). The delta (post-pre=Δ) between the situations before and after the treatment was used to compare groups using a one-way ANOVA with pos hoc Tukey tests. The Statistica for Windows Release 7 software (Statsoft Inc., Tulsa, OK) was used for the statistical analysis, and the significance level was set at 5 % ($p<0.05$).

Results

The mean value of the grip strength did not differ significantly for any of the groups [placebo group—from 19±3 to 19±4 kgf; US + LLLT group—from 19±5 to 19±4 kgf and; TE + US + LLLT group—from 16±4 to 17±3 kgf ($p \geq 0.05$)]. The results of PPT and topographical maps can be seen in the Figs. 3 and 4, respectively. The average PPT shows significant decrease of the pain sensitivity for both the US + LLLT group and the TE + US + LLLT group.

Discussion

This is the first study evaluating the long-term synergic effects of US and LLLT in women with hand osteoarthritis. The main finding of this study was an increase of the pain threshold after 3 months of treatment. There was no placebo effect.

US alone generates pain relief [12, 13], through modulation of nerve conduction velocity and increasing a nociceptive threshold. The US also changes the muscular contractility and reduces spasms [9]. These factors may increases hand function [13]. In parallel, phototherapy alone also induces pain relief via alteration in the mitochondrial membrane potential, modulation of nociception, changing in nerve conduction velocity with decreased number of sensory impulses per unit of time, increasing production of serotonin and beta-endorphins, generating antioxidant effects, and reducing inflammatory mediators such as prostaglandin E2 and cytokines. In addition, the modulations of the synaptic transmission generate effects of muscle relaxation [25, 26].

The effective results depend of clinical trial's protocol. Brosseau et al. [16] investigated the effects of LLLT on pain, stiffness, and grip strength in hand osteoarthritis, but there was no significant difference for these parameters between LLLT and placebo groups. Meireles et al. [27] also found no significant difference for pain and range of motion after treatment with LLLT on the hands of patients with rheumatoid arthritis. However, Ekim et al. [28] show that LLLT was effectives for pain and hand function in patients with rheumatoid arthritis with carpal tunnel syndrome. Other studies show that LLLT

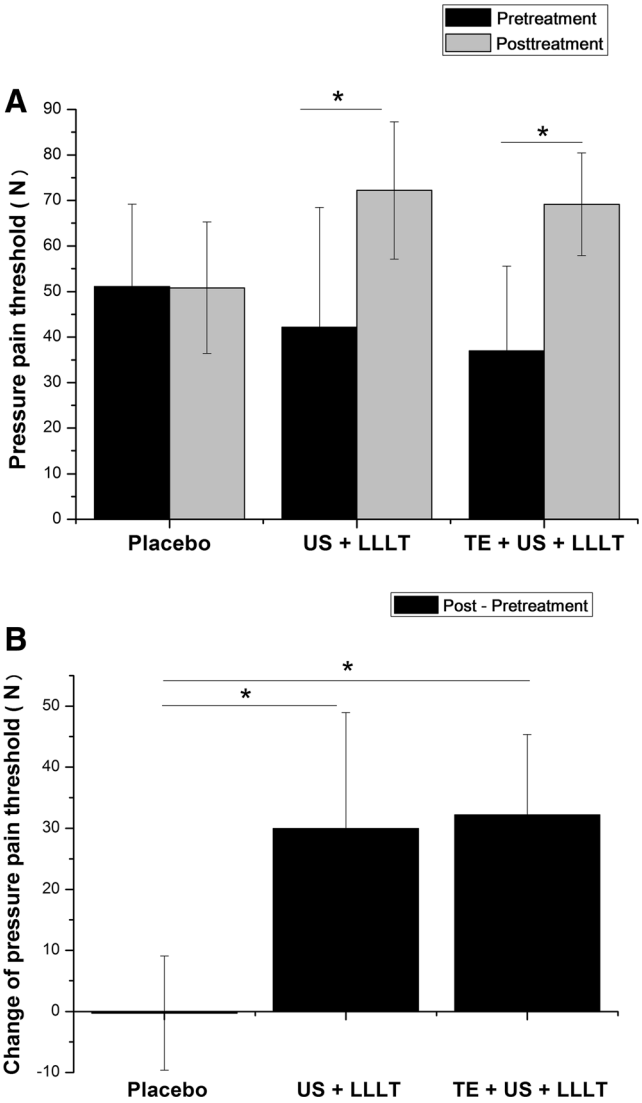

Fig. 3 Average pressure pain threshold (PPT). Results obtained for the PPT are significantly higher for both the US + LLLT and TE + US + LLLT groups (intragroup differences) (**a**). The changes in the average PPT between baseline and 3 months showed significant intergroup differences (**b**). *$p<0.001$

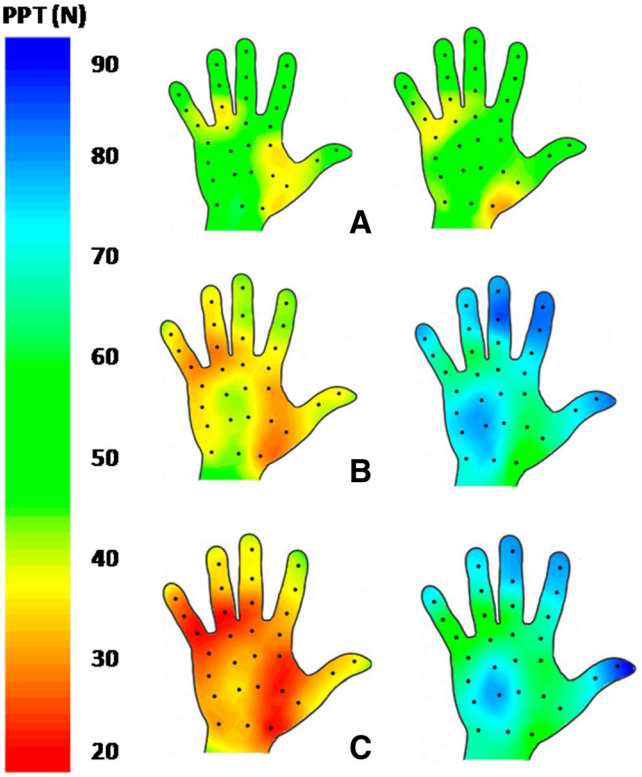

Fig. 4 Pressure pain sensitivity topographical maps. Pretreatment (*right*) and posttreatment (*left*) for placebo group (**a**), US + LLLT group (**b**), and TE + US + LLLT group (**c**). The color schemes for PPT values measured at 30 points on dominant hand can be observed. The *red to yellow color schemes* (lower PPT levels) indicated pressure hyperalgesia and the *green to blue color schemes* (PPT levels increased) indicated less sensitivity to pain after 3 months, mainly for both the US + LLLT group and the TE + US + LLLT group

have also been effective for treatment of carpal tunnel syndrome [14, 15].

These results are controversial and may be related to laser parameters used. The lack of understanding of dose (J/cm^2) and energy (J), as well as types of laser and wavelength may lead to error in the parameters used, and no effect of treatment for rheumatic diseases [29, 30]. The dosage recommendations of the World Association for Laser Therapy (WALT) states a total of 4 J per finger joint and total of 8 J for a wrist (www.walt.nu). On the other hand, new geometries of devices may explain the differences in the adopted parameters, especially when the parameters are compared with the dosage recommendations of the WALT. Although we applied high energy, the scanning mode (noncontact) was used, leading to small energy loss. However, deep penetration of infrared radiation in biological tissue is well known. It is estimated that the infrared laser irradiation on skin may show a 1/e penetration over 2 cm [31, 32]. This kind of penetration adequate assures quantity of light reaching the inflammation spots during treatment. Moreover, study that used US plus laser suggested the improvement of light penetration by US [33]. Photoacoustic diagnostic systems show laser and US at 90° [34] or 360° [35] or positioned side by side [36] also to improve light penetration and image quality. Al-Habib et al. [33] measured the amount of infrared laser power that passed the skin, muscle, and bone of rats with or without US effect using the Beer-Lambert law equation. The results showed power output of the laser increased when US was added to various tissue thicknesses indicating light deep penetration. Although this recent study has showed that ultrasonic irradiation together with infrared irradiation may increase light penetration, this is a topic out of the scope of our current study.

Regarding our protocol, the prototype has simple manipulation and great effectiveness reducing the time of therapeutic session and leading to economical advantages, because it

includes US together with LLLT. For these reasons, we do not use US and after, LLLT.

In addition, US plus LLLT may potentiate therapeutic effects, as evidenced by bone healing accelerated [33, 37]. In the study of Otadi et al. [11], the therapeutic effects were more evidenced when US and LLLT were associated with exercise for the management of shoulder tendonitis. However, in our study, the therapeutic exercise did not provide additional effect in grip strength of the women with hand osteoarthritis. Probably, both exercise load and training volume were lower and insufficient to improve grip strength. In contrast, US or LLLT has been effective to promote anti-inflammatory effect [9, 17] with analgesia alleviating symptoms of OA [11, 12, 14, 15], and so, therapeutic exercises can be performed without difficulties. Futures studies should include measurements of range of motion (ROM) and hand functionality to develop a better understanding of rehabilitation process in hand osteoarthritis.

Regarding to US, Akinbo et al. [38] applied US plus anti-inflammatory drugs (phonophoresis) and physical exercise for treatment of knee osteoarthritis. The authors found significant improvements in pain, stiffness, and physical function. However, Akinbo et al. [38] used continuous ultrasonic waves (predominant thermal effects), but we choose pulsed ultrasonic waves (predominant nonthermal effects), because according to in vitro [39] and animal models [40], as well as clinical trials [12, 13, 19, 41], the pulsed mode generates improvement of cartilage repair as well as anti-inflammatory and analgesic actions without damaging the patients with acute joint inflammation due to thermal effects.

For pain analysis, we used mechanically evoked pain by algometer to determine PPT measures. This is a useful popular model for inducing acute experimental pain and provides highly reliable measures of PPT [42]. According to Fernández-de-Las-Peñas et al. [24], PPT mapping is a new imaging modality of pain sensitivity that enables visualization of nonuniformity in pressure pain sensitivity and consequently, deep tissue hyperalgesia in a specific location of the body.

The PPT increased for both US + LLLT and TE + US + LLLT groups indicate desensitization of mechanonociceptors caused by pain modulation [43]. The current results about pain relief might be due to the effects of US plus LLLT prototype. Then, this prototype may induce its antinociceptive effect through central neuromodulatory mechanisms (central desensitization). Some factors can influence in antinociceptive effect [44], such as physiologic (biochemical and electrochemical), spinal (segmental), and supraspinal mechanisms. Temporal summation of pain in humans is presented as an increased pain perception in response to repetitive stimulation of the same stimulus intensity, including skin, muscle, and joint structures [45]. Several therapeutic modalities or physical agents may induce temporal summation of somatic pain, for example, neuromuscular electrical stimulation, LLLT, thermotherapy (cold, superficial heat, or contrast) [46], microwaves [47], radiofrequency [48], US [44], and body vibration [49]. In this context, the synergic effects of US and LLLT may generate temporal summation of pain and analgesia for long term.

Regarding the limitations of this study, we did not perform other control groups with individual treatments, for example, US alone and LLLT alone used in a scanning mode, both applied with the same parameters of our prototype. Moreover, the penetration of light in the presence of the US was also not investigated in our study. Future studies should be done to investigate (i) the penetration of light with and without US effect through a phantom, ex vivo, or in vivo studies and (ii) the effects of the US and LLLT, separately, on the pain relief and hand rehabilitation.

Conclusion

The new device combines the therapeutic effects of both US and LLLT. These positive effects lead to an increase of the pain threshold in women with hand osteoarthritis. Then, there was long-term decrease in pain sensitivity. Moreover, there was no placebo effect. In this context, we considered that the US associated with LLLT can be potentially used for physical rehabilitation and sports protocols where the main objective is a pain relief.

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