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EDITORIAL

Editor again! Other challenges!

Novamente editor! Outros desafios!

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As editor of *Revista Dor: Pesquisa Clínica e Terapêutica* from 2009 to 2012, with the support of the authors, the editorial board and the boards of the Brazilian Society for the Study of Pain, I had the privilege of having the collaboration of the authors, reviewers and members of the technical staff, index the journal in LILACS, Scielo and Latindex.

As of January 2018, *Revista Dor: Pesquisa Clínica e Terapêutica* was renamed Brazilian Journal of Pain (BrJP), to provide greater international visibility since scientific journals with English titles are accessed by the entire scientific community, as this is the language used internationally in events and scientific publications.

Now, as the new editor of the BrJP for the 2020-2021 biennium, and feeling the enormous responsibility of the position, I address you, authors and reviewers, to share the objectives to be pursued in this biennium.

The most relevant is to improve the quality, both from an ethical and scientific point of view, of BrJP, a scientific journal aimed mainly at health professionals; researchers, professionals, educators, administrators, and students, interested in the study and treatment of pain.

Another objective is to make the necessary adjustments in the management of BrJP to adapt it to the standards required for indexing on other platforms such as Medline, which is the main database of online bibliographic citations of the NLM Pubmed system, used internationally to provide access to the literature of biomedical journals in the world.

In order to achieve this objective, the policy and scientific quality of the BrJP will be considered, weighing the objectivity, credibility, and quality of the content, through the analysis of the article selection methods, the explicit review process by external peers, adherence to ethical guidelines, disclosure of financial conflicts of interest, correction of errata, explicit retractions, and opportunity for comments and differing opinions to be presented.

To achieve these objectives, the collaboration of the authors is essential by sending original articles, carefully prepared, following the standards of good research practice in humans and animals; preparing review articles carefully following the universal rules for the elaboration of this type of scientific article; and sending well-written clinical cases that make it possible to advance in the study and treatment of pain.

The cooperation of all members of the editorial board is also crucial, carrying through the review of the articles sent, quickly and in-depth, elaborating comments that can improve the content and the form of the text and the author.

The main objective is that each issue of the BrJP is eagerly awaited for being a scientific journal that offers relevant, easy-to-read content that brings new information to those who seek to understand and explain the intriguing mechanisms of pain to improve pain control techniques of their patients, in addition to perfecting and stimulating reasoning and scientific production.

The responsibility that has been entrusted to me is enormous and I am not sparing efforts to live up to the trust of the community that granted me this mission that honors me very much, and you can rest assured that I will do my utmost to take the BrJP to a high scientific level.

In order to face these challenges, I count on your collaboration.

Prof. Dr. Irimar de Paula Posso
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The influence of the cannabinoid receptor CB1 on the periaqueductal gray in mice treated with photobiomodulation after chronic constriction injury of the sciatic nerve: a placebo-controlled trial

Influência do receptor canabinóide CB1 na substância cinzenta periaquedutal em camundongos tratados por fotobiomodulação após constrição crônica do nervo ciático: ensaio controlado por placebo

Gabriela Xavier Santos[1], Giovane Galdino de-Souza[1], Suélen Santos Alves[1], Gabriela Nagai Ocamoto[1], Nivaldo Antônio Parizotto[2], Luciana Maria dos-Reis[1]

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ABSTRACT

BACKGROUND AND OBJECTIVES: Studies have demonstrated that the cannabinoid CB1 receptor is involved in the modulation of pain, mainly by activating the descending pain control pathway. However, the role of photobiomodulation in this process is not well elucidated. Thus, the present study aimed to investigate the involvement of the CB1 receptor in the supraspinal photobiomodulation-induced antinociception.

METHODS: Male albino swiss mice were submitted to chronic constriction injury and treated with photobiomodulation. To evaluate the supraspinal involvement of the CB1 receptor in the photobiomodulation-induced antinociception, the cannabinoid CB1 receptor antagonist AM251 (0.1µg/vol 0.2µL) was injected 5 minutes before the photobiomodulation treatment. The photobiomodulation treatment was performed on the fifth day after the stereotactic surgery and chronic constriction injury at a dose of 50J/cm^2 in acute condition. The hot plate and von Frey monofilaments tests were performed to evaluate the thermal and mechanical pain sensitivity, respectively.

RESULTS: The thermal and mechanical nociceptive threshold was higher in mice with chronic constriction injury, injected with saline and treated with photobiomodulation at the dose of 50J/cm^2 in both the hot plate ($p<0.001$) and von Frey ($p>0.001$) tests. These antinociceptive effects were not detected in mice with chronic constriction injury pre-treated with AM251.

CONCLUSION: The present study suggests that CB1 receptors located in Supraspinal structures, participate in the control of neuropathic pain following photobiomodulation treatment in animals undergoing chronic constriction injury.

Keywords: Cannabinoid, Lasers, Pain, Receptors, Rehabilitation.

RESUMO

JUSTIFICATIVA E OBJETIVOS: Estudos demonstraram que o receptor canabinóide CB1 está envolvido na modulação da dor, principalmente pela ativação da via descendente de controle da dor, porém o papel da fotobiomodulação nesse processo não é bem elucidado. Assim, o presente estudo teve como objetivo investigar o envolvimento do receptor CB1 na antinocicepção induzida pela fotobiomodulação a nível supraespinhal.

MÉTODOS: Camundongos machos suíço albinos foram submetidos à lesão por constrição crônica e tratados com fotobiomodulação. Para avaliar o envolvimento supraespinhal do receptor CB1 na antinocicepção induzida por fotobiomodulação foi injetado o antagonista do receptor canabinóide CB1, AM251 (0,1µg/vol 0,2µL) 5 minutos antes do tratamento com fotobiomodulação. O tratamento de fotobiomodulação foi realizado no quinto dia após cirurgia estereotática e lesão por constrição crônica, na dose de 50J/cm^2 em estado agudo. Os testes de placa quente e monofilamentos de *von Frey* foram realizados para avaliar a sensibilidade térmica e mecânica à dor, respectivamente.

RESULTADOS: O limiar térmico e mecânico nociceptivo foi maior nos camundongos com lesão por constrição crônica, injetados com solução salina e tratados com fotobiomodulação na dose de 50J/cm^2 nos testes de placa quente ($p<0,001$) e von Frey ($p>0,001$). Esses efeitos antinociceptivos não foram detectados em camundongos com lesão por constrição crônica tratados com AM251.

CONCLUSÃO: O presente estudo sugere que os receptores CB1 localizados nas estruturas supraespinhais participam do controle da dor neuropática, após tratamento com fotobiomodulação em animais submetidos à lesão por constrição crônica.

Descritores: Canabinóide, Dor, Lasers, Reabilitação, Receptores.

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INTRODUCTION

Neuropathic pain is defined as the pain arising as a direct consequence of a lesion or disease affecting the somatosensory system either at the peripheral or central level, even in the absence of nociception[1,2].

The neuropathic pain is maladaptive and does not have biological importance. It is a significant cause of permanent incapacity, mainly when it becomes chronic. Patients usually present spontaneous pain, allodynia, and hyperalgesia and do not respond well to many types of treatment. They may also present comorbidities, such as depression, anxiety, sleep disorders, and, consequently, lower quality of life[3-5].

Pain transmission in the spinal cord is modulated by supraspinal structures, such as periaqueductal gray (PAG), which makes the neuronal connection with the locus coeruleus (LC). The LC, in its turn, is connected to the rostral ventromedial medulla (RVM), which sends projections to the dorsal horn of the spinal cord through the dorsolateral spinal funiculus. This pathway results in the inhibition of the nociceptive information[6,7]. Moreover, the pain caused by lesions in the peripheral nervous system and modulated by the PAG are more likely related to different systems, such as the endocannabinoid system[8,9].

The endocannabinoid system consists of cannabinoid receptors 1 (CB1) and 2 (CB2), their endogenous binders, and enzymes that catalyze their biosynthesis and degradation[10]. The CB1 receptors are present mainly in the central nervous system, especially in regions related to transmission and pain modulation, such as PAG, RVM, the dorsal horn of the spinal cord, and other motor and limbic structures. On the other hand, the CB2 receptors are located mainly in the peripheral nervous system, but not exclusively[11].

Among the most widely used therapies to treat neuropathic pain are the pharmacological approaches. However, these treatments are not efficient all the time in many patients[12]. Therefore, numerous studies have focused on the search for new therapeutic strategies for the treatment of neuropathic pain. Photobiomodulation (PBM) using low-level laser therapy (LLLT) has been investigated as an alternative treatment for treating this chronic condition.

PBM is a low-cost and non-invasive approach with few contraindications and side effects[13]. Studies have demonstrated positive effects of PBM on neuropathic pain relief in both humans[14-16] and animal models[17,18].

The peripheral attenuation of pain by PBM occurs through two distinct mechanisms: (1) the light interacts directly with neuron promoting the temporary inhibition of the axonal transport in small nerve fibers (A δ and C)[19] and (2) the light may induce anti-inflammatory effects that reduce the oxidative stress and increase the synthesis of ATP by the activation of a cascade of metabolic effects, reducing proinflammatory cytokines, such as prostaglandins and interleukins leading to decrease the activation of nociceptors[20].

However, the involvement of supraspinal structures in pain control after peripheral PBM application has not been clearly elucidated in the published studies. Therefore, the objective of our study is to identify the influence of the CB1 receptor on the dorsolateral column of the periaqueductal gray (dlPAG) in mice treated with photobiomodulation after chronic constriction injury (CCI) of the sciatic nerve.

METHODS

The study was designed as a placebo-controlled trial. The protocols for animal studies were performed in accordance with the IASP and the Brazilian College of Animal Experimentation (COBEA).

Initially, 35 male swiss albino mice (35-40g) were used in this study. However, seventeen animals were excluded based on the following criteria: the cannula did not hit the dlPAG; the mice removed its cannula, and there was no reduction in the nociceptive threshold after CCI. Therefore, eighteen animals were included and divided into 3 groups: (1) CCI+PBM 0J/cm^2, (2) CCI+PBM 50J/cm^{2,} and (3) CCI+SALINE+50J/cm^2 with 6 animals in each group. They were kept under controlled conditions (on a 12h light-dark cycle and temperature at 23±2°C). Mice were given *ad libitum* access to food and water and they were transferred to the habituation room at least one hour before the experimentation.

Surgical procedures

First, the mice were anesthetized intraperitoneally (i.p.) with ketamine (0.5mL, Dopalen® Brasil), xylazine (0.25mL, Anasedan® Brasil), and saline (3.0mL), to a total volume of 0.1mL/kg. Posteriorly, the mouse head and right hind leg (region close to the sciatic nerve anatomical course) were shaved and cleaned with iodine. Then, the animals were positioned in a digital stereotaxic apparatus (Stoelting Co, wood dale, United States). After a 1cm long incision, we removed all soft tissue from the surface of the skull for the cranium implantation of a stainless-steel 7mm 26G guide cannulas leading to the dlPAG. We also placed a dummy into the guide cannula to reduce the risk of occlusion and infection.

The stereotaxic coordinates used for cannula implantation were established as per Franklin and Paxinos: - 4.1mm posterior to bregma; - 1.4mm lateral to the midline, and – 2.3mm ventral to skull surface[21].

After the cannula implantation, we induced the neuropathic pain through CCI[22]. With the mouse still anesthetized in the stereotaxic apparatus and lying on its chest, an incision was made 3-4mm below the femur, and the connective tissue between the gluteus superficialis and the biceps femoris muscles was cut, enabling clear visualization of the sciatic nerve. Then, we performed the constriction of the right sciatic nerve, tying four ligatures with a double knot, using a non-inflammable sterile mononylon 6.0 with stereotaxic angle at 26°.

Next, the animals were placed in their own cages and monitored until they recovered from anesthesia. A period of 5 days was considered for surgery recovery, and the animals were monitored daily until the end of the experiment for signs of infection.

Drug preparation and injection

The influence of the CB1 receptor on the dlPAG was analyzed through the injection of the cannabinoid CB1 receptor antag-

onist AM251 (0.1µg – TOCRIS® USA) (N-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide) diluted in saline solution (0.9%) with 2% of Dimethyl Sulfoxide (DMSO) or saline.

The injection of AM251 in dlPAG was given 5 days after the surgical procedure. An 8mm 33G injection needle (1.0mm beyond the tip of the guide cannula) was connected to a 5µL Hamilton microsyringe (Hamilton Company®) via a polyethylene tube (PE-10). The needle was introduced into the cannula for the injection of 0.2µL for 45 seconds. The movement of a small bubble air in the PE-10 was observed to confirm the successful injection of the drug[23].

Application of photobiomodulation with low-level laser therapy

The device used for PBM was the LASER HTM COMPACT® (HTM indústria de Equipamento Eletroeletrônico Ltda, Amparo, São Paulo, Brasil). The mice were subject to irradiation with infrared aluminum gallium arsenide (AsALGa) laser with 830nm, continuous wavelength, fluence of 50J/cm^{2,} and output power of 30mW, following a standard protocol[24].

The PBM was applied immediately after the injection of the drug in dlPAG. For this procedure, the animals were gently handled to avoid stress and the laser pointer was positioned perpendicular to the skin over the CCI area. We performed a single radiation with a dose of 50J/cm^2 for 300 seconds using the punctual technique. The total size of the radiated area was 1cm^2.

The mice were randomly divided into 3 groups with 6 animals per group: (1) PBM radiation at the dose of 0J/cm^2, laser OFF, and injection of AM251 (CCI + PBM 0J/cm^2 + AM251); (2) PBM radiation at the dose of 50J/cm^2, laser ON, and injection of AM251 (CCI + PBM 50/cm^2 + AM251). The control group, (3) PBM radiation at dose of 50J/cm^2 with laser ON, and injection of saline (CCI + PBM 50J/cm^2 + SALINE).

After the PBM radiation, the animals were allocated in the von Frey apparatus for acclimatization. After 30 minutes of acclimatization, the hot plate test and von Frey testing were initiated.

Nociceptive tests

The hot plate test[24] was used for the evaluation of thermal hyperalgesia. The animals were placed on a 48ºC (47.8-49.4ºC) hot plate (Insight®, Brasil). The latency, time necessary, for the response to the pain stimulus (hind-paw lick, jump etc.) was recorded. In the absence of a reaction, the mice were removed from the hot plate at 30 seconds to avoid tissue injury, and 30 seconds latency was recorded as the response.

The von Frey[5] monofilaments were used for the evaluation of mechanical hyperalgesia. Mice were placed in a plastic cage suspended above a wire mesh grid and allowed to move freely and acclimatize to the testing apparatus for 30 minutes before the experiments. The von Frey monofilaments (Aesthesia®, EUA) were pressed against the plantar surface of the right paw. A positive response was noted if the paw was sharply withdrawn upon the application of the monofilament. We performed three measures of the nociceptive threshold for each animal, separated by 3-minute intervals. The mean of the three measurements was recorded as the mechanical paw withdrawal threshold.

The hot plate test and von Frey testing were performed at three time points: (1) before the surgical procedure (baseline), (2) on the fifth day, prior to the drug infusion and PBM radiation, and (3) also on the fifth day, 30 minutes after the drug injection and PBM radiation (Figure 1). Animals that did not demonstrate a significant reduction in the sensory threshold (compared with the values obtained at baseline) were excluded.

Histological verification of cannula placements

After the completion of all the procedures, the cannula placement was histologically examined. To this end, the mice were anesthetized intraperitoneally with ketamine (0.5mL), xylazine (0.25mL), and saline (3.0mL), to a total volume of 0.1mL/kg. Next, the mice received injections of polyethylene blue, following the same protocol described previously. Then, the mice were euthanized, and their brains were removed and immersed in 10% formalin for fixation. The brains were frozen, and sections were cut at 40µm on a freezing microtome (Lupetec®, Brasil). The samples were analyzed through a microscope (Biolab®, Brasil). The visualization of the methylene blue dispersion indicated the cannula placement. The animals whose cannula did not reach the dlPAG were excluded.

This study was also submitted and approved by the Ethical Committee for the Use of Animals of the Federal University of Alfenas (CEUA- UNIFAL- MG/Brasil – protocol number 09/2016).

Statistical analysis

The data are presented as mean±S.E.M. the statistical analysis of behavioral experiments, we performed the two-way variance analysis (ANOVA) followed by the Bonferroni post hoc test for multiple comparisons, being considered statistically significant values of $p<0.01$. Statistical analysis and preparation of figures were performed using GraphPad Prism Software, Version 5 (GraphPad Software, La Jolla, CA).

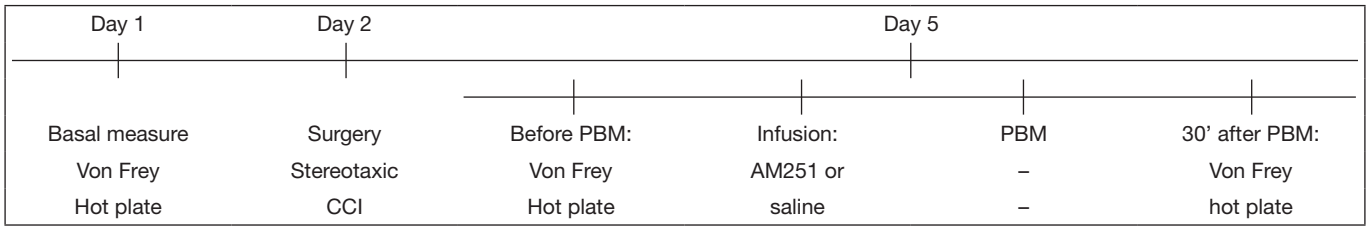

Figure 1. Timeline representation of the experimental protocol
CCI = chronic constriction injury; PBM = photobiomodulation using low-level laser therapy; AM251 = (N-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide)- Cannabinoid CB1 receptor antagonist.

RESULTS

Figure 2 shows the results concerning the thermal nociceptive threshold assessed by the hot plate test. We observed that after the CCI there was a reduction of the nociceptive thermal threshold in all the evaluated groups ($p<0.001$) compared to baseline. After irradiation with PBM, a significant increase of the nociceptive thermal threshold in the (3) CCI + PBM 50J/cm^2 + saline group (23.5±1.87) was observed when compared to the (1) CCI + PBM 0J/cm^2 + AM251 group (14.08±1.07) ($p<0.001$), showing antinociceptive effect of 50J/cm^2 PBM and there was no effect of AM251 on the nociceptive threshold. The AM251 reversed the analgesic effect of the PBM as observed in the comparison between the groups (3) CCI + PBM 50J/cm^2 + saline (23.5±1.87) and (2) CCI + PBM 50J/cm^2 + AM251 (12.76±0.87) ($p<0.001$).

Figure 3 shows the results concerning the mechanical nociceptive threshold assessed by the von Frey test. We observed that after the CCI there was a reduction of the mechanical nociceptive threshold in all the evaluated groups ($p<0.001$) compared to baseline. After irradiation with PBM, a significant increase of the nociceptive thermal threshold in the (1) CCI + PBM 50J/cm^2 + saline group (1.065±0.071) was observed when compared to the (2) CCI + PBM 0J/cm^2 + AM251 group (0.49±0.06) ($p<0.001$), showing antinociceptive effect of 50J/cm^2 PBM and no effect of AM251 on the nociceptive threshold. The AM251 reversed the analgesic effect of PBM as observed in the comparison between the groups (1) CCI + PBM 50J/cm^2 + saline (1.065±0.071) and (2) CCI + PBM 50J/cm^2 + AM251 (0.50±0.07) ($p<0.001$).

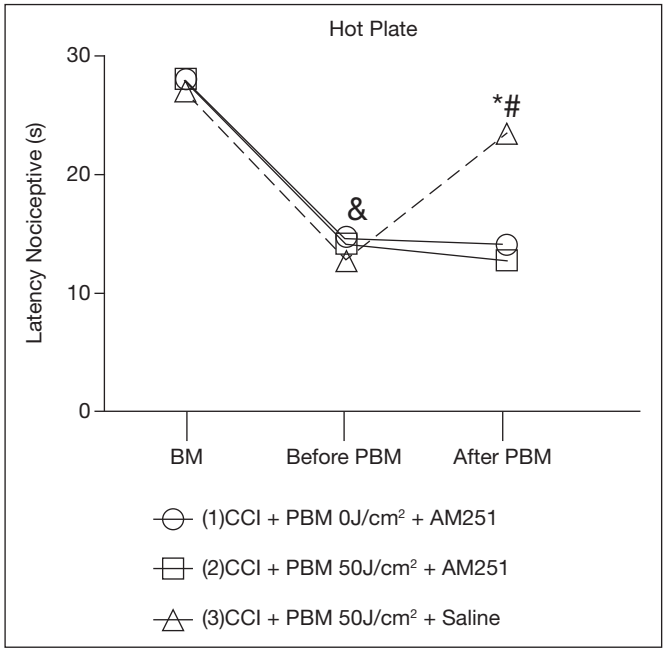

Figure 2. Effect of PBM 50J/cm^2 or 0J/cm^2 with intra-lateral periaqueductal gray side injection (I.dlPAG) of CB1 receptor antagonist AM251 or saline on thermal nociceptive latency of paw withdrawal, by the test of the hot plate.
CCI = chronic constriction injury; Moments of measurement: BM = baseline measurement of nociceptive threshold; Before PBM = threshold measurement before application of PBM, After PBM = measurement of threshold after PBM application. The data represent the mean±SD of the mean; values of $p<0.01$ were considered significant.

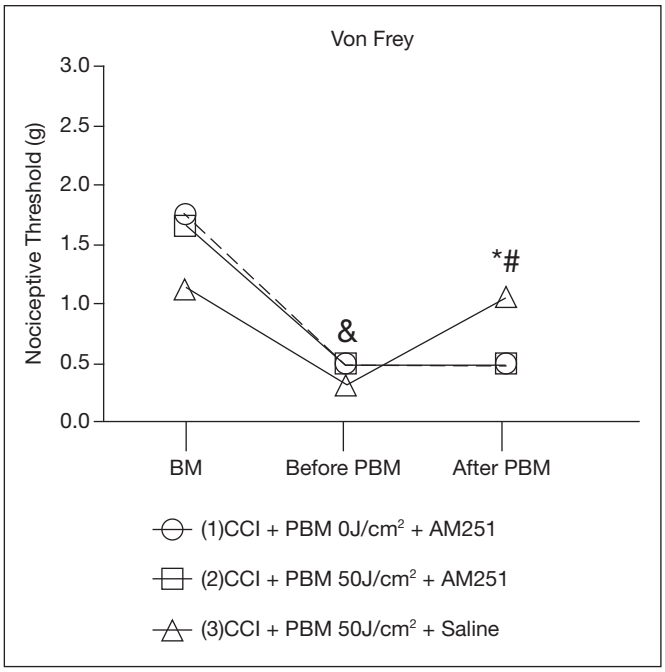

Figure 3. Effect of the PBM 50J/cm^2 or 0J/cm^2 associated with intra-lateral periaqueductal gray matter infusion (I.dlPAG) of CB1 receptor antagonist AM251 or saline on the mechanical nociceptive threshold of paw withdrawal, by the test of filaments of Von Frey.
CCI = chronic constriction injury; Moments of measurement: MB = baseline measurement of the nociceptive threshold; Before PBM = threshold measurement before application of PBM; After PBM = measurement of threshold after PBM application. The data represent the mean±SD of the mean; values of $p<0.01$ were considered significant.

DISCUSSION

In the present study, all groups showed a reduction in the nociceptive threshold, when compared to the baseline, evaluated by the hot plate test and the von Frey test, aligning with the previous studies[22,24,25]. An increase in nociceptive threshold was observed in the group (2) CCI+PBM 50J/cm^2 + saline when compared with baseline values after application of 50J/cm^2 PBM, showing good results for the treatment of neuropathic pain. Most of the previous studies showed beneficial effects even with a large variation in creep, from 1J/cm^2 to 1312J/cm^2 [14]. A recent study[24] used the PBM with wavelength 808nm and varied fluences of 10, 20, and 40J/cm^2 in order to establish a therapeutic window. The results showed that only higher fluences 20 and 40J/cm^2 were able to produce β-endorphin increase and effectively reduce neuropathic pain, corroborating with the results of the present study.

The local peripheral effect of PBM is widely described in the literature. Hsieh et al.[25] demonstrated that PBM applied transcutaneous at the CCI site reduces the levels of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), and hypoxia-inducible factor 1α (HIF-1α) leading to improved hypoxia/tissue ischemia. It elevates the levels of endothelial growth factor (VEGF) and nerve growth factor (NGF), resulting in improvement of functional recovery, nerve regeneration and analgesia. Another study observed the reduction of the proinflammatory cytokines Fractalkine (FKN) and IL-1β, and the reduction of the glial satellite cells in the dorsal root ganglion,

causing pain relief and reduced paw protection behavior behavior in animals with neuropathy and treated with PBM[26].

Moreover, previous studies reinforce that the PBM provides improvement in the sciatic functional index in animals with neuropathy[27,28], accelerates nerve regeneration[29-31], increases the expression of the neuronal growth marker GAP 43 related to the process of regeneration[32], increased number of myelinated fibers, improved electrophysiological function, and increased vascular network and collagen[33].

In the present study, it was possible to observe the participation of the CB1 receptor of PAG in the antinociceptive effect after PBM, since the antagonization of these receptors by AM251, a selective antagonist of CB1 receptors, in the PAG, was able to reverse the antinociceptive effect of PBM 50J/cm^2.

Although CNS structures play a crucial role in the modulation of neuropathic pain, there is a scarcity in the literature of data proving the involvement of supraspinal structures, especially regarding PAG, in the antinociceptive effect mediated by PBM. Similarly, the endocannabinoid system, especially the CB1 receptor, has been related to the modulation of neuropathic pain[8,9]. However, little is known about the participation of these receptors in supraspinal structures, such as PAG, in the modulation of neuropathic pain disorders by PBM.

A study[34] showed that the intracerebroventricular and systemic administration of selective agonist of CB1 receptors, ACEA ([N-(2-chloroethyl) 5, 8, 11, 14-eicosaetraenamide]), promotes the reduction of acute and chronic mechanical allodynia in mice submitted to brachial plexus avulsion. However, this antinociceptive effect was better observed in the activation of the central pathway.

Another study reinforces the involvement of the supraspinal structures in pain control by the endocannabinoid system when performing drug infusion CP-55.940 and WIN55,212-2 (cannabinoid receptor agonist) in the lateral ventricle, an increase in the latency in the tail-withdrawal test[35]. In a model of neuropathic pain induced by chemotherapy, the antinociceptive effect was observed, in face of the mechanical and thermal allodynia stimulus, by inhibiting endocannabinoid resorption and its Degradation (FAHH), however, after antagonizing the receptors of CB1 or CB2, the effect provided by the inhibition of FAHH[8] was completely blocked. Concerning the dlPAG, a study demonstrated that it is related to the analgesic effect induced by stress, assessed by the tail test and that this effect is mediated by the activation of the CB1 receptors, through its endogenous ligand anandamide and 2- Araquidonylglycerol (2-AG)[36] reinforcing the results found in this study.

It is possible to suggest the participation of the CB1 receptor in supraspinal structures, specifically of the dlPAG, in the effect of pain modulation after treatment with PBM in mice submitted to CCI, which makes the study pertinent since in the literature is not well Elucidated if the application of the PBM peripherical involves the participation of the CNS.

Studies aimed at understanding the mechanisms of action of resources used in clinical practice are relevant as they strengthen evidence-based practice. New studies with agonist drugs and inhibitors of endogenous endocannabinoid degradation are necessary to better elucidate the analgesia processes by the PBM.

CONCLUSION

According to the data presented, it is suggested the participation of the CB1 receptors in the dlPAG, in the antinociceptive effect promoted by the PBM by laser of gallium arsenide aluminum (AsAlGa) wavelength of 830 nanometers, continuous and with radiant power maximum and average of 30mW in the intensity of 50 J/cm^2, after chronic constriction of the sciatic nerve.

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Low-level laser therapy in periarticular morphological aspects of the knee of Wistar rats in rheumatoid arthritis model

Laser de baixa intensidade nos aspectos morfológicos periarticulares do joelho de ratos Wistar em modelo de artrite reumatoide

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ABSTRACT

BACKGROUND AND OBJECTIVES: The deleterious effects of rheumatoid arthritis on periarticular tissues have not yet been fully elucidated. Therefore, the search for treatments that can modulate the inflammatory profile and tissue remodeling is pertinent. The present study evaluated the effects of low-level laser therapy (LLLT) on the morphology of periarticular tissues and synovial membrane of rats in a rheumatoid arthritis model.
METHODS: Sixty-four male rats were divided into acute (7 days) and chronic (28 days) inflammatory periods, with four groups (n=8) each, being: CG (control group), LG (lesion group), CLaG (laser control group) and LLaG (laser lesion group). The animals of the lesion groups received two inoculations of Freund's Complete Adjuvant at a concentration of 50µL, the first at the base of the tail, and the second at the right knee. The animals in the control groups were injected with isotonic sodium chloride solution. The ClaG and LLaG were treated with 660nm LBI, 5J/cm^2 in the right knee. After the experimental period, the animals were euthanized, and the knees were processed for light microscopy.
RESULTS: The CG and CLaG morphological analysis had normal aspects. The LG showed synovitis, femur, and tibia with changes in the periosteum, with inflammatory cells and bone modifications. In the LLaG, the synovial membrane showed signs of improvement. Bone tissue in the chronic period showed morphological aspects, denoting tissue remodeling.
CONCLUSION: The experimental model was efficient in simulating inflammatory tissue events, and the low-level laser therapy showed beneficial effects on the morphology of the periarticular tissues.
Keywords: Knee joint, Laser therapy, Rheumatoid arthritis.

RESUMO

JUSTIFICATIVA E OBJETIVOS: Os efeitos deletérios da artrite reumatoide nos tecidos periarticulares ainda não estão totalmente elucidados, sendo pertinente a busca por tratamentos que possam modular o perfil inflamatório e a remodelação tecidual. O presente estudo avaliou os efeitos do laser de baixa intensidade (LBI) na morfologia dos tecidos periarticulares e membrana sinovial de ratos submetidos à um modelo de artrite reumatoide.
MÉTODOS: Para tanto, 64 ratos machos foram divididos em períodos inflamatórios agudo (7 dias) e crônico (28 dias), com 4 grupos (n=8) cada, sendo: GC (grupo controle), GL (grupo lesão), GCLa (grupo controle laser) e GLLa (grupo lesão laser). Os animais dos grupos lesão foram submetidos a duas inoculações de Adjuvante Completo de Freund na concentração de 50µL, sendo a primeira na base da cauda e a segunda no joelho direito. Os animais do grupo controle foram submetidos a injeções com solução isotônica de cloreto de sódio. Os grupos GCla e GLLa foram tratados com LBI 660nm, pontual no joelho direito, 5J/cm^2. Após o período experimental, os animais foram eutanasiados e os joelhos processados para análises em microscopia de luz.
RESULTADOS: Na análise morfológica, GC e GCLa apresentaram aspectos normais. O GL apresentou sinovite, fêmur e tíbia com alterações no periósteo, com células inflamatórias e modificações ósseas. A membrana sinovial mostrou sinais de melhora no GLLa. No período crônico, o tecido ósseo apresentou aspectos morfológicos, denotando remodelação tecidual.
CONCLUSÃO: O modelo experimental foi eficiente em simular os eventos inflamatórios teciduais, e o laser de baixa intensidade apresentou efeitos benéficos sobre a morfologia dos tecidos periarticulares.
Descritores: Articulação do joelho, Artrite reumatoide, Terapia a laser.

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INTRODUCTION

Rheumatoid arthritis (RA) is characterized as an inflammatory, systemic, autoimmune disease that affects joint tissue and periarticular structures[1]. Symmetry is a fundamental feature

of the disease that evolves from asymmetric to symmetrical, with the progression of pathological manifestations. Initial inflammatory events affect the synovial membrane, presenting cellular hyperplasia and intense inflammatory process, denoting synovitis[2].

The synovial membrane has innervation marked by the presence of positive nerve fibers for proinflammatory neuropeptides, such as substance P (sP) and calcitonin gene-related peptide (CGRP), both in the intimal and subintimal layers and around the blood vessels[3]. Such neuropeptides are the result of antidromic nerve conduction, reaching the affected joint causing progeny effects of chronic inflammatory joint processes, characterized by neurogenic inflammation[4]. The injurious stimulus, together with the onset of inflammation triggered by events of the immune system, such as that occurring in RA, sensitize the primary nociceptive neurons, and in response, the exacerbation of pain and inflammation occurs.

Among the features of conservative treatments used to control pain and modulation of inflammatory events is the Low-Intensity Laser (LIL). This therapy is effective in stimulating wound healing, reducing the inflammatory process and analgesia, and the primary target of irradiated light is cytochrome C oxidase, located in mitochondria. The interaction results in increased metabolism, leading to signal transduction to other cell regions[5] favoring tissue repair.

The use of physical resources may be associated with other therapies already established for inflammatory control of the disease, characterized by joint cartilage degradation and inflammation of periarticular tissues, leading to reduced functional capacity, and pathological signs found in patients with RA[6]. However, LIL has different effects on tissues according to the parameters of use, such as dose, wavelength, and application site.

Studies on the deleterious effects of RA on the synovial membrane are scarce, and little is known about these actions on periarticular bone tissue. Moreover, as these important structures are involved in joint function, the specificity of conservative treatments that can modulate the inflammatory profile and periarticular tissue remodeling is relevant to enable the maintenance of the function and the quality of life of individuals affected by the disease that has a chronic character.

The hypothesis of the study is that the disease may induce tissue effects beyond the synovial fluid, but also in adjacent tissues such as the synovial membrane and peripheral bone region. Also, check whether LIL, due to its properties, demonstrates beneficial effects on these tissues. Given the above, this study aimed to evaluate if the LIL has effects on the morphology of the periarticular tissues of rats submitted to experimental rheumatoid arthritis.

METHODS

The study was an experimental and randomized study, composed of 64 male *Wistar* rats, 15 weeks old, weighing 300±19g, kept in polypropylene plastic boxes, with *ad libitum* access to food and water, temperature-controlled at 21°C±1°C, and 12-hour light/dark photoperiod.

The animals were randomized using the *Microsoft Excel* 2016 software and separated into two inflammatory periods of the disease, acute (7 days of inflammation) and chronic (28 days of inflammation). They were further subdivided into four groups each, CG (control group), IG (injury group), LaCG (laser control group), and LaIG (laser injury group) (Figure 1).

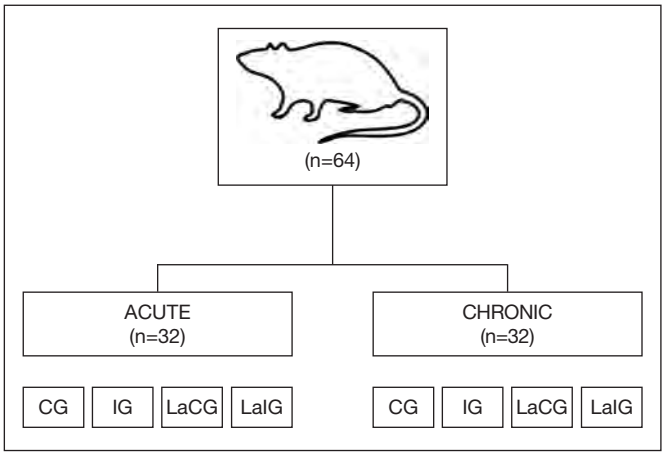

Figure 1. Diagram of sample groups
Source: Author.
CG = control group; IG = injury group; LaCG = laser control group; LaIG = laser injury group.

Experimental model of rheumatoid arthritis induced by Freund's Complete Adjuvant

Initially, the animals underwent a pre-sensitization protocol[7] by intradermal inoculation at the base of the tail of 50µL of FCA (Freund's Complete Adjuvant, Difco®, 0.5mg/mL, Mycobacterium butirycum) for the animals of IG and LaIG, or 0.9% physiological solution (PS), Aster® for CG, and LaCG animals. To this end, the substance administration area was shaved and submitted to asepsis of the injection site with 1% iodized alcohol (Rialcool®). Then the animals were injected with a 1mL syringe and 13x4.5mm needle. The needle was inserted approximately 1cm into the base of the tail subcutaneously. This intradermal injection procedure was the first inflammatory stimulus seven days before the intraarticular injection.

Intraarticular injection of 50µL (0.5mg/mL) of FCA or PS was administered to the right tibiofemoral joint of the animals. The animals were contained manually. The anterior knee area of the right pelvic limb was shaved, and asepsis was performed with 1% iodized alcohol. Then the injection was given with a 1mL syringe and 13x4.5mm needle.

Treatment Protocol

The animals of groups LaCG and LaIG received the treatment with LIL[5,8] (Laserpulse - Ibramed®), in the knee region of the sensitized pelvic limb. The application points were anterior to the patella, medial face in the tibiofemoral joint, lateral face in the tibiofibular joint, and posterior in the popliteal region. The treatment parameters were: four-point point technique, 660-nanometer wavelength, 30mW power, spot area: 0.06cm^2, energy density: 5J/cm^2 per point, time per point: 10 seconds, energy total per point: 0.003J, totaling four applications in animals of

the acute group, and 14 applications in animals of the chronic inflammatory period in intercalated days. The equipment was checked for potency before treatment began.

Morphological analysis

After the experimental period, animals from acute (7 days of inflammation) and chronic (28 days) inflammatory period were euthanized by guillotine decapitation, previously anesthetized with an intraperitoneal injection of ketamine hydrochloride (Ketalar® - Brazil, 95mg/kg) and xylazine (Xilazin® - Brazil, 12mg/kg). After checking the animal's state of consciousness (observed due to the lack of motor response to the tail pinch and interdigital folds), the right and left knee joints were dissected, reduced in tibial and femoral transverse sections and fixed in methacarn (70% methanol, 20% chloroform, 10% glacial acetic acid) for 48 hours. Then the pieces were set in 70% alcohol (Neon®) for 15 days.

The material was washed for 24 hours in running water. The joints were decalcified in 5% trichloroacetic acid (Neon®) for seven days, following a routine histological procedure for inclusion in paraffin (Alphatec®). Sagittal plane sections were performed on Olympus CUT 4055 microtome, 7µm thick, and mounted on glass slides. For staining, hematoxylin and eosin protocol (Synth®) was used. The slides were analyzed under a light microscope and photomicrographed under an Olympus® DP71 (USA) microscope. In the morphological analysis, normal aspects and changes in the synovial membrane and bone periarticular region of the femur and tibia were observed (Figure 2).

The Committee of Ethics in the Use of Animals (CEUA) of the State University of the West of Paraná (UNIOESTE) approved this study on 10/27/2017.

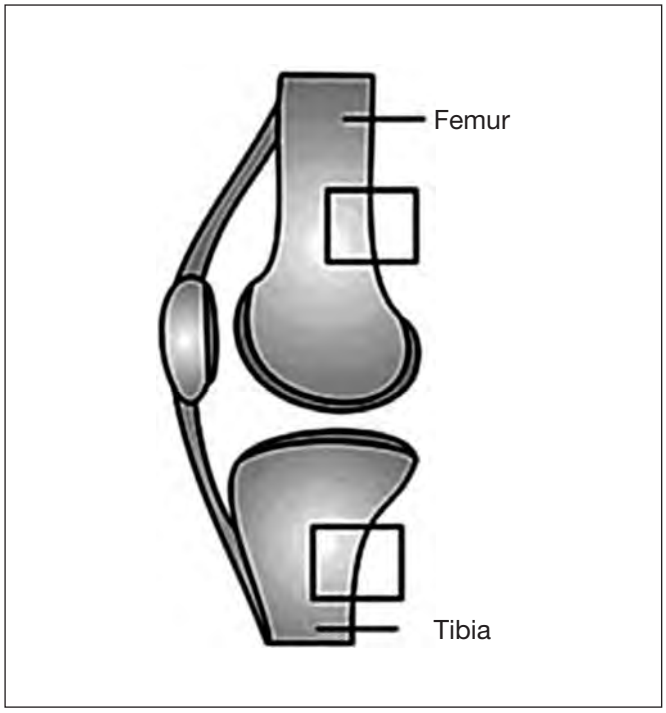

Figure 2. Diagram of the knee joint, showing the periarticular analysis sites of the femur and tibia (demarcated field)

RESULTS

The morphological analysis of the CG synovial membrane (Figure 3A, B, C, D) presents normal aspects of the synovial membrane organized in two layers of cells (synoviocytes) in the synovial intima, and subintima, with a predominance of adipose cells, blood vessels and connective without changes. LaCG animals (Figure 3I, J, K, L) presented similar morphological aspects to CG.

However, the synovial membrane of IG animals (Figure 3C, D, E, F) revealed an intense inflammatory process, with disorganized synovial intima thickening as to the epithelioid distribution of synoviocytes. Subintima with the absence of adipocytes, increased number of blood vessels, characterizing synovial joints. In LaIG (Figure 3I, J, K, L), the synovial membrane showed discrete cell organization and adipocyte reorganization, showing tissue recovery.

In acute IG animals (Figure 3F), the left pelvic limb (non-sensitized) showed morphological changes in the synovial membrane, which was not observed in animals in the chronic group, which maintained normal morphological aspects in the non-sensitized limb.

In the analysis of the periarticular region of the femur (Figure 4) and tibia (Figure 5) of the animals of the control group (A, B, C, D), normal aspects of the bone tissue were verified, with periosteum in its osteogenic and fibrous layers, bone matrix with the appearance of compact bone and presence of blood vessels.

In the animals of IG (E, F, G, H), in the femur (Figure 4) and tibia (Figure 5), there were morphological differences compared to the CG, the tissue presents with intense inflammatory process in the periosteum, in the osteogenic layer, presence of differentiated inflammatory cells, gaps and modification of the compact bone in the bone matrix region to a feature of spongy bone.

Periarticular morphological modifications were found with greater evidence in both the femur and tibia of animals in the acute group, still presenting alterations in the non-sensitized contralateral limb (Figure 4).

Femur and tibia of LaIG animals (F, G, H, I), in the acute period, presented morphological aspects similar to IG. In the chronic period, there was tissue remodeling with morphological similarities to the CG.

DISCUSSION

In this study, two inoculations of FCA containing Mycobacterium butyricum induced the appearance of significant morphological changes, including synovial membrane hyperplasia with feature synovitis and periarticular bone modifications in the femur and tibia. A study postulated that adequate RA induction consists of two injections of FCA containing an attenuated mycobacterium, considering the classification of the disease, autoimmune, the model is used through pre-sensitization of animals[7].

The pathogenesis of RA can be influenced by the inflammatory potentials of spinal cord[8]. Stimuli such as mechanical trauma, pH changes, presence of inflammatory mediators, can trigger a process called neurogenic inflammation[9], which reflects the release of neurotransmitters from the primary afferent, such as

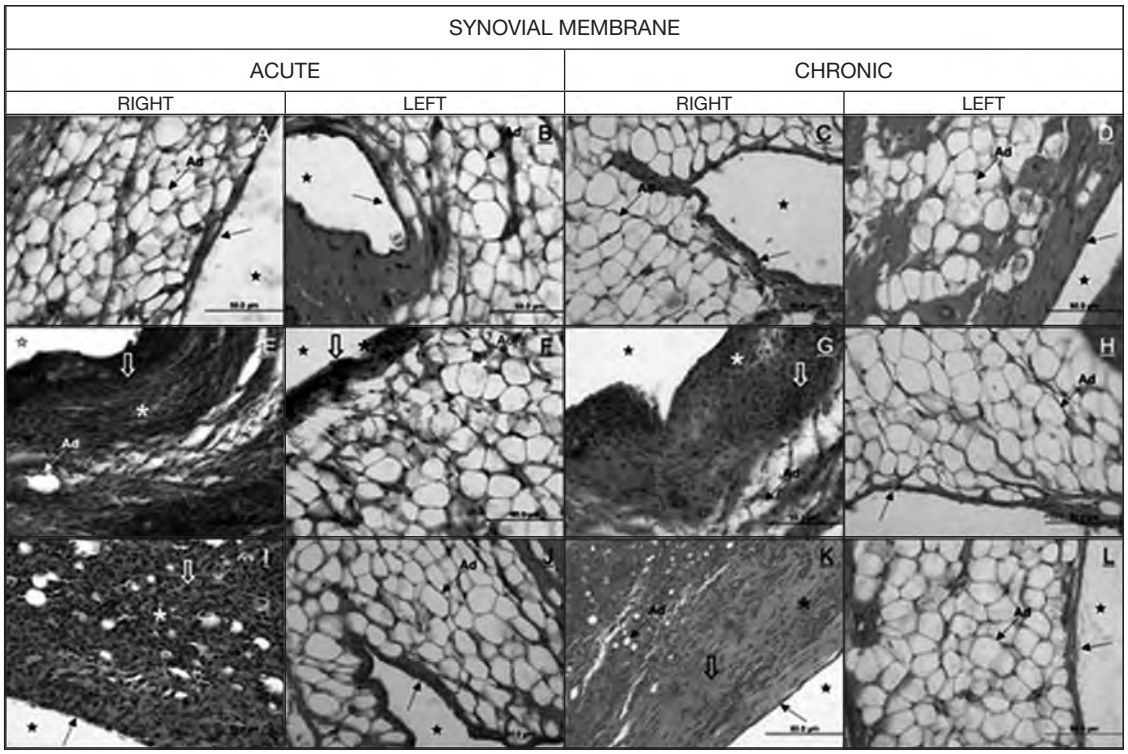

Figure 3. Photomicrographs of the synovial membrane, periods of acute and chronic inflammation, right and left limbs, respectively. Sagittal section, hematoxylin, and eosin staining. **CG** (A, B, C, D) shows normal aspects of the two-layered synovial membrane, the synovial intima, with synoviocytes distributed in layers (arrow), subintima organized with a predominance of adipocytes (Ad), joint cavity (star) without inflammatory infiltrate. In **IG** (E, F, G, H), the synovial membrane with an intense inflammatory process (hollow arrow), thickening of the synovial intima (asterisk), and decrease of the adipose cells (Ad) in the subintima. In **LaIG** (I, J, K, L) acute inflammatory period denotes tissue recovery with slight adipocyte reorganization.

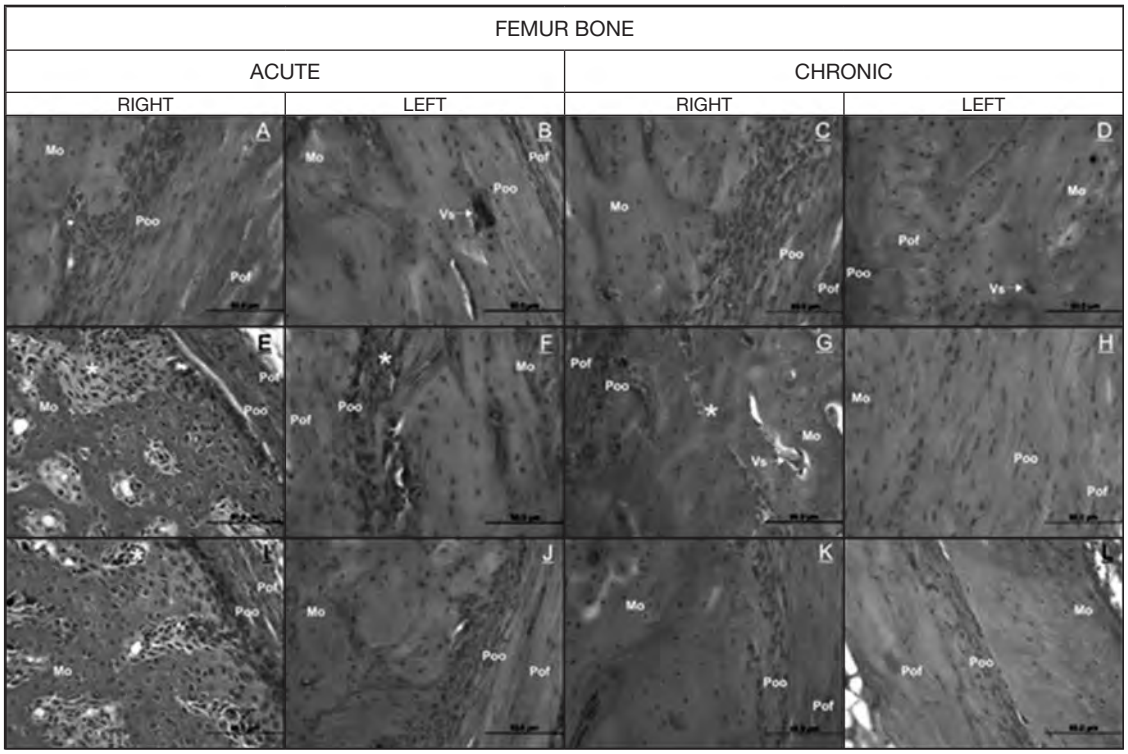

Figure 4. Photomicrographs of the femur, periarticular peripheral region, acute and chronic inflammatory period, right and left respectively. Longitudinal section, hematoxylin, and eosin staining. **CG** (A, B, C, D) normal aspects of bone tissue, periosteum in its fibrous (Pof), osteogenic (Poo), and bone matrix (Mo) layers with the presence of blood vessels (Vs). **IG** (E, F, G, H) tissue denotes the presence of inflammatory cells and modification of compact bone to feature of spongy bone (asterisk). **LaIG** (I, J) in the acute inflammatory period, have morphological aspects similar to IG, with the onset of tissue remodeling. In **LaIG** chronic inflammatory period (K, L) reveals similarities to **CG** with tissue remodeling.

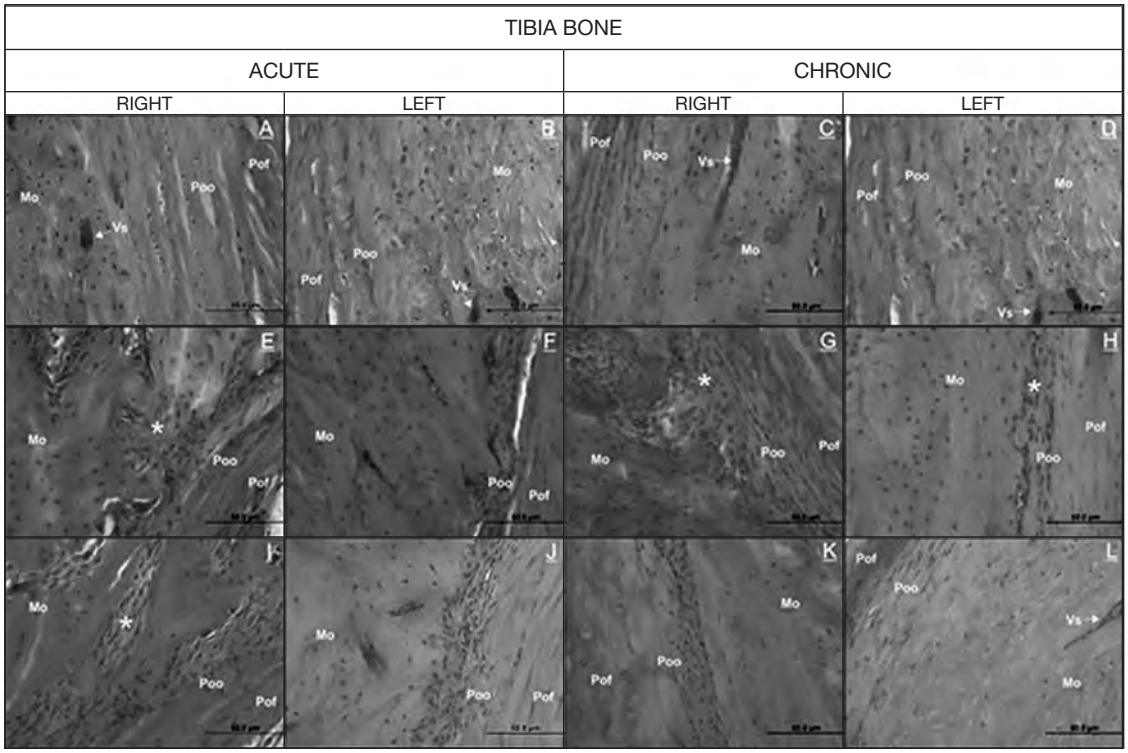

Figure 5. Photomicrographs of the tibia, periarticular peripheral region, acute and chronic inflammatory periods, right and left, respectively. Longitudinal section, hematoxylin, and eosin staining. **CG** (A, B, C, D) normal aspects of bone tissue, periosteum in its fibrous (Pof) and osteogenic (Poo) layers, bone matrix (Mo) with the presence of blood vessels (Bv). **IG** (E, F, G, H) tissue denotes the presence of inflammatory cells and modification of the compact bone to spongy bone feature (asterisk). **LaIG** (I, J), the acute inflammatory period, has morphological aspects similar to IG. **LaIG** in the chronic inflammatory period (K, L), show similarities to the CG with tissue remodeling.

sP and CGRP[10], which enhance peripheral inflammation. One study has inferred that a sensitive nerve contralateral to arthritis induction, leads to action potentials towards the periphery; also observed that animals induced to an inflammatory process by FCA, presented greater spontaneous antidromic activity when compared to a control group. In their study, they found that the contralateral joints showed plasma leakage due to the presence of sP and CGRP, reaffirming the neuronal action in the formation of the symmetrical lesional pattern of RA[11]. In this study, it was found that the synovial membrane and bone tissue of the non-sensitized pelvic limb in IG animals showed aspects of cell hyperplasia.

Another study demonstrated that LIL suppresses the signaling of afferent fibers and modulates synaptic transmission to neurons in the dorsal horns, and inhibition of sP, supporting the neural mechanisms of the effectiveness of laser therapy in painful conditions[12]. The synovial membrane is innervated by positive sP fibers, which indicates that it is the inflammatory stimulus that potentiates RA[3]. The results found in this study corroborate the other findings that demonstrated laser therapy actions in reducing synovial membrane hyperplasia[13]. In the same vein, a systematic review to evaluate the effectiveness of LIL in the treatment of RA concluded that the therapy has a beneficial effect when used for at least four weeks, with effects in reducing pain and morning stiffness, symptoms reported by affected patients[14].

The tissue initially affected by inflammation in RA is the synovial membrane, denoting cellular hyperplasia, and an inflammatory process that characterizes the synovitis process[2]. The animals in the injury groups showed morphological changes with an intense inflammatory process. In cases of disease progression without proper treatment, inflammatory events progress to other tissues, with joint destruction and bone loss.

Periarticular bone changes in RA patients are caused by bone increase and resorption resulting from the accumulation of inflammatory cells, including lymphocytes and macrophages, and pro-inflammatory cytokines that promote osteoclast-mediated bone resorption. Qualitative changes in periarticular bone in RA are poorly studied, but of great interest, as affected patients are prone to fractures due to tissue fragility caused by bone loss[15]. In this study, the morphology of the bone tissue of the femur and tibia in the periarticular region of rats submitted to experimental RA was evaluated. It was found that IG animals showed bone changes resulting from an intense inflammatory process.

Histopathological analyses have shown a significant reduction in inflammation, bone destruction, cartilage, and pannus formation with other forms of therapy[16]. However, there is no clinical evidence regarding the relationship between LIL and periarticular bone analysis. The decrease in bone strength associated with chronic inflammation, together with significant changes in bone quality and structure, can increase bone susceptibility to failure under low energy load[17].

The animals that were treated with LIL in the bone morphological aspects in the chronic inflammatory period showed tissue remodeling. It is suggested that the treatment provided an increase in me-

tabolism, in addition to modulation of the inflammatory process in the experimental period. LIL causes vasodilation, a relevant factor for joint inflammation, as it increases local oxygen support and contributes to the migration of immune cells[18] helping tissue repair[19-23]. A study that evaluated the effects of LIL on the modulation of the inflammatory process, using an experimental model with animals, concluded that the treatment has better effects when administered in the chronic phases of the disease[19]. They also infer that the 660 nm wavelength is the most suitable in this phase and that a treatment plan of three sessions, with an interval of 1 day between them, is sufficient to modulate the inflammatory profile of the disease. In this study, it was found that the 660 nm wavelength stimulated discreet cell organization and reorganization of adipocytes, denoting tissue recovery.

LIL has differentiated actions on tissues, according to the parameters of use, such as dose, wavelength, continuous or pulsed mode, duration and place of treatment, and anti-inflammatory effects when used in disease progression[19,20]. The therapy has biostimulating properties, causing increased cellular metabolism, collagen synthesis, analgesic, and anti-inflammatory effects[5,21]. According to a study, the use of the 670nm wavelength showed satisfactory results as an expression of vascular endothelial growth factors[22]. In this study, the wavelength used was 660nm and showed tissue morphological improvement when compared to animals in the IG[22].

The initial hypothesis of the study was to verify whether the experimental model of disease induction reflected in morphological changes in periarticular tissues and to evaluate whether treatment with LIL would be effective in reducing the harmful effects of the injury. However, the hypothesis can be confirmed due to the changes found in the animals of the injury groups, which denotes an intense periarticular inflammatory process. The LIL has also been shown to be effective in morphologically reducing these effects, even if it does not promote tissue restoration. Also, the study is limited by the protocol with male animals, and the prevalence in humans is in the female gender[24-27].

It is suggested to conduct studies specifically related to bone tissue morphometry to corroborate the morphological findings of this study. Still, other LIL parameters, such as intensity, dose and wavelength, should be tested, so that the findings can be used in the clinical practice.

CONCLUSION

The LIL showed beneficial effects on the morphology of the periarticular tissues of rats submitted to experimental rheumatoid arthritis.

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Effects of duloxetine, fluoxetine and pregabalin on fentanyl-induced hyperalgesia in rattus novergicus

Efeitos da duloxetina, fluoxetina e pregabalina sobre a hiperalgesia induzida por fentanil em rattus novergicus

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ABSTRACT

BACKGROUND AND OBJECTIVES: Opioids are drugs used to relieve pain, but may cause increased pain sensitivity, known as opioid-induced hyperalgesia, which adversely affects pain management. This study aimed to check if fentanyl, an opioid widely used in the clinical practice, produces hyperalgesia that can be attenuated by duloxetine, fluoxetine and pregabalin.

METHODS: Thirty male Wistar rats were divided into six groups. The animals in group 1 received 1mL of 0.9% saline solution intraperitoneally (IP) and gavage; group 2 received fentanyl at a dose of 100μg.kg^{-1} IP and 0.9% saline solution per gavage; groups 3, 4 and 5 received fentanyl at the dose of 100μg.kg^{-1} IP, and gavage with duloxetine, 40mg.kg^{-1}, fluoxetine, 40mg.kg^{-1} and pregabalin, 40mg.kg^{-1}, respectively. Under general anesthesia with isoflurane, all animals were submitted to plantar surgical incision. The application of Von Frey filaments assessed hyperalgesia at the second hour, one, three, five and seven days after treatment.

RESULTS: Two hours after the procedure, no differences were observed between G1 and G2, although G3, G4, and G5 showed less hyperalgesia. On day one and day three, a greater hyperalgesic effect was observed in G2 when compared to G1, G3, G4 and G5. On day five, there was a hyperalgesic effect on G2, and on day seven, there were no differences among the groups.

CONCLUSION: The results suggest that fentanyl induces hyperalgesia and the efficacy of duloxetine, fluoxetine, and pregabalin in reducing it.

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Keywords: Duloxetine, Fentanyl, Fluoxetine, Hyperalgesia, Pregabalin, Rats.

RESUMO

JUSTIFICATIVA E OBJETIVOS: Opioides são fármacos utilizados para o alívio da dor, porém, podem causar aumento da sensibilidade dolorosa, denominada hiperalgesia induzida por opioides, que afeta negativamente o tratamento da dor. O objetivo deste estudo foi avaliar se o fentanil, opioide amplamente utilizado na prática clínica, produz hiperalgesia que pode ser atenuada pela duloxetina, fluoxetina e pregabalina.

MÉTODOS: Trinta ratos Wistar machos, foram divididos em 6 grupos. No grupo 1, os animais receberam 1mL de solução fisiológica (SF) a 0,9% por via intraperitoneal (IP) e por gavagem; no grupo 2, fentanil na dose de 100μg.kg^{-1} IP e SF a 0,9% por gavagem; nos grupos 3, 4 e 5 os animais receberam fentanil na dose de 100μg.kg^{-1} IP e, por gavagem, receberam respectivamente duloxetina, 40mg.kg^{-1}, fluoxetina, 40mg.kg^{-1} e pregabalina, 40mg.kg^{-1}. A avaliação da hiperalgesia e sua atenuação foi feita pela aplicação de filamentos de Von Frey, na 2ª hora e nos dias 1, 3, 5 e 7, após o tratamento.

RESULTADOS: Na 2ª hora pós-procedimento não foram observadas diferenças entre G1 e G2, entretanto, G3, G4 e G5 se mostraram com menor hiperalgesia. No 1º e 3º dias foi observado maior efeito hiperalgésico em G2 quando comparado com G1, G3, G4 e G5. No 5º dia foi observado efeito hiperalgésico no G2, e no 7º dia não houve diferenças entre os grupos.

CONCLUSÃO: Os resultados sugerem que o fentanil induz hiperalgesia e eficácia da duloxetina, fluoxetina e pregabalina na sua redução.

Descritores: Duloxetina, Fentanil, Fluoxetina, Hiperalgesia, Pregabalina, Ratos.

INTRODUCTION

Pain is one of the most important and complex human experiences, associated with actual or potential tissue damage, and its treatment with opioids has increased substantially in recent years, making it's prescription common in the United States[1,2]. However, the increase in prescriptions has been causing many problems, among which are the lack of knowledge regarding long-term efficacy, abusive use and adverse events associated with prolonged use, including opioid-induced hyperalgesia (OIH), a

phenomenon for which paradoxically, opioids can induce or sensitize patients to acute pain[3,4]. In this sense, patients who receive high doses of opioids may experience severe acute pain after surgery, with an increased dose of analgesics, and anxiety for both the patient and the physician[4].

The mechanisms proposed to be responsible for OIH are multiple, including changes in N-methyl-D-aspartate (NMDA) receptors and second messengers, spinal cyclooxygenase (COX) activation, the release of excitatory amino acids, reduction of inhibitory neurotransmitters, descending facilitation and the anti-analgesic system[2,3,5,6].

The increased release of glutamate in the dorsal horn of the spinal cord and the consequent sustained increase in stimulus and response of NMDA receptors by removal of magnesium mediated by protein kinase-C seem to be important mechanisms involved in OIH[7]. These NMDA receptors can be activated by opioids, which act as excitatory neurotransmitters facilitating calcium intake into the cell and central sensitization (CS). Calcium intake causes increased protein kinase-C activity, phosphorylation, and inactivation of opioid receptors, in addition to an increase in nitric oxide synthase[8].

OIH has been associated with an increase in cholecystokinin, a calcitonin gene-related peptide (CGRP), substance-P, and nociception in the rostral ventromedial medulla due to increased expression of excitatory opioid receptors, to the detriment of inhibitory opioid receptors[5,9,10].

The descending facilitatory pathways, mediated by opioids, located in the rostral ventromedial medulla, also seem to be involved in OIH due to neuroplastic changes, since exposure to morphine causes neuroplastic changes in the rostral ventromedial medulla, with increased release of dynorphin and primary afferents fiber neurotransmitters[3,6,11]. In this way, the administration of opioids would cause an increase in dynorphin, which may favor OIH[5,6].

There is evidence that spinal dynorphin is pro-nociceptive, causing the release of excitatory neurotransmitters from primary afferent neurons, suggesting positive feedback, amplifying the sensory afferents[6]. In addition, prostaglandins, cytokines, and chemokines may also be relevant in the development of OIH, since opioids activate the release of cytokines, with increased C-fos protein in sensory neurons in the spinal cord. Other systems that may be involved in OIH with reduced glycinergic inhibitory control are nitric oxide synthase and heme oxygenase[2,3].

Studies in rodents have demonstrated that fentanyl cause OIH and suggested that the protein kinase Iiα (CaMKIIα) dependent of $Ca2^{+}$/calmodulin in the lateral capsular division of the central nucleus of the amygdala (CeLC) and the spinal cord can play a key role in the modulation of the OIH[12,13].

The duloxetine, an antidepressant from the class of serotonin--norepinephrine reuptake inhibitors (SNRI), is indicated for the treatment of depressive disorder, generalized anxiety disorder, and chronic pain conditions as diabetic neuropathic pain, chronic fibromyalgia and chronic musculoskeletal pain[14].

The role of serotonin and norepinephrine in the regulation of mood occurs through the ascending neuronal pathways, starting from the middle portion of the brain, extending to the limbic system and the prefrontal cortex. Besides, noradrenergic and serotonergic projections from the brain stem descend through the spinal cord, where it is believed to be involved in the regulation of somatosensory perception. Alterations in the serotonergic and noradrenergic pathways modify both the cerebral perception of the sensory stimuli of the ascending pathways, as well as alter the mechanism of pain inhibition by the descending pathways. Depression and chronic pain share these neuronal serotonergic and noradrenergic pathways, which is why duloxetine has been shown to be effective in these two conditions[15].

Duloxetine has been shown to be effective in chronic pain conditions such as fibromyalgia, peripheral diabetic neuropathy, painful symptoms of knee osteoarthritis, and chronic low back pain. There is also evidence of relief from painful symptoms associated with depression and generalized anxiety disorder[16].

The effect of fluoxetine on the serotonergic system (SRI) is well known, making evident the use of fluoxetine as a treatment option for different chronic pain conditions such as fibromyalgia, chronic tension-type headache, migraine without aura, painful diabetic neuropathy, musculoskeletal pain, chronic pelvic pain, and coronary syndrome[17]. Due to the effects of SRI by elevating serotonin in the central nervous system (CNS), it is postulated that duloxetine and fluoxetine may be useful in attenuating OIH.

The involvement of glutamate neurotransmission in synaptic plasticity suggests that pregabalin may also be useful in attenuating OIH[18], being a GABA analog drug, which selectively binds with high affinity to the calcium channels, widely distributed in the CNS and peripheral, producing a modulating effect with a reduction of the excessive release of several excitatory neurotransmitters.

Several clinical trials have documented its effect on pain relief and quality of life, including mood and sleep disorders, and are, therefore, indicated for the treatment of fibromyalgia, neuropathic pain, and generalized anxiety disorder[18,19].

Pregabalin has been shown to be effective in treating fibromyalgia, with improvement in various sleep parameters. Pain reduction was evidenced, regardless of anxiety or depression symptoms, suggesting that the pain reduction caused by pregabalin results mainly from the direct effect of the treatment, and not the indirect effect from the improvement of anxiety and depression symptoms[20].

Behavioral tests such as the application of von Frey filaments and thermal hyperalgesia have been used to evaluate hyperalgesia in rats[21]. In this study, the test with von Frey filaments was used to assess whether fentanyl, an opioid widely used in clinical practice, produces hyperalgesia that may suffer interference from the drugs duloxetine, fluoxetine, and pregabalin.

METHODS

For the characteristics of the animal sample and convenience, it was used 30 male Wistar rats, weighing between 220 and 300g, allocated in number of 5 animals per compartment, where they remained for 15 days before the beginning of the experiment for adequate adaptation, treated with balanced commercial feed and water "ad libitum," 12-hour light-dark cycle and room temperature ranging between 19 and 25°C.

The IASP Ethical Standards, which regulates experiments carried out in animals (Committee for Research and Ethical Issues of the IASP, 1983), were followed to conduct the experimental procedures. All experiments were carried out at the Laboratory of Pharmacology and Physiology at the University of Taubaté, SP.

To obtain mild anesthesia, the animals were placed in a 15x25x-15cm transparent glass chamber with a transparent cover to allow the visualization of the animal, with a hole in the front and back to enable oxygen (O_2), anesthetic gases and carbon dioxide, entering and exiting, respectively. The halogenated agent used in anesthetic induction was isoflurane (Isoforine®, Cristália, Itapira, Brazil), at a concentration of 4.0% in fraction of inspired oxygen (FiO_2) of 1.0, administered by a calibrated vaporizer (Hospital HB) and maintained for three minutes, time necessary for the animal to present loss of postural reflexes and inability to move in the chamber. Then, the animal was removed from the chamber and placed with the snout in a mask through which it received 4% isoflurane in O_2 as in the anesthesia induction chamber.

The surgical procedure consisted of a 1.0cm long, longitudinal surgical incision in the right posterior paw, according to the postoperative pain model[21]. This incision was made with a scalpel with blade number 11, incising the skin and the plantar fascia region of the paw, starting 0.5cm from the edge of the calcaneus and extending towards the toes. Then, the plantar muscle was elevated and incised longitudinally, with its insertion intact. After hemostasis with slight pressure on the surgical area, all planes were approached and sutured with two separate stitches with 4-0 mono nylon needle thread.

The animals were randomly divided into six groups to receive similar volumes of drugs or 0.9% saline solution (SS). In group 1, the animals received 1mL of 0.9% SS by intraperitoneal (IP) and gavage; group 2 fentanyl (100μg.kg^{-1}) (IP) in a single dose and 0.9% SS by gavage; Group 3 fentanyl (100μg.kg^{-1}) (IP) in a single dose and duloxetine (40mg.kg^{-1}) by gavage; group 4 fentanyl (100μg.kg^{-1}) (IP) in a single dose and fluoxetine (40mg.kg^{-1}) by gavage and group 5 fentanyl (100μg.kg^{-1}) (IP) in a single dose and pregabalin (40mg.kg^{-1}) by gavage.

The evaluation of hyperalgesia was performed by applying the von Frey[21] filament test. The animals were kept in a wooden chamber, with a 0.5cm checkered galvanized fabric floor. A mirror was attached under the floor to allow the researcher to observe the application of the filament and the reflex of limb removal. Before applying the filament, the animals were kept in the box for about 15 minutes for adaptation. Each of the filaments, in an ascending pressure order, was applied three times in a row with an interval of 3 to 5 seconds, moving on to the next filament, being considered a positive response when the animal removed the support of the injured limb from the floor by the application of the filament. It was considered zero pressure value when the animals presented the limb fully retracted; that is, there was no need for any stimulus for the animal to collect the limb support. The collected data were recorded on a specific data collection form for each animal at the following times: 2nd hour, 1, 3, 5 and 7 days after the surgical procedure and treatment administration.

The project started after the approval by the Ethics Committee on the Use of Animals CEUA/UNITAU, under No. 03/2017.

Statistical analysis

The JMP® software from the SAS (Statistical Analysis System) Institute was used, applying the Student's *t*-test, comparing pair by pair, and adopting a significance level lower than 5% ($p<0.05$).

RESULTS

When comparing the average weight of the animals before the beginning of the experiment, there was no statistically significant difference between groups ($p<0.05$). In the 2nd hour after the surgical procedure, the pain intensity, assessed by von Frey filaments, is shown in figure 1, showing that there is no significant difference when comparing G1 with G2 ($p=0.3759$), but with statistical significance when they were compared to groups G3, G4, and G5 ($p<0.05$).

On the first day after the surgical procedure, the pain intensity, assessed by von Frey filaments, is shown in figure 2, showing a significant difference between G1 and G2 ($p <0.05$) and between these and groups G3, G4 and G5 ($p<0.01$).

On the third day after the surgical procedure, the pain intensity, assessed by von Frey filaments, is shown in figure 3, showing a significant difference between the G1 and G2 ($p<0.05$) and, between these and groups G3, G4 and G5 ($p<0.01$).

On the 5th day after the surgical procedure, the pain intensity, assessed by von Frey filaments, is shown in figure 4, showing a significant difference between G2 and groups G1, G3, G4, and G5 ($p<0.05$).

On the 7th day after the surgical procedure, the pain intensity, assessed by von Frey filaments, is shown in figure 5, showing a significant difference between groups.

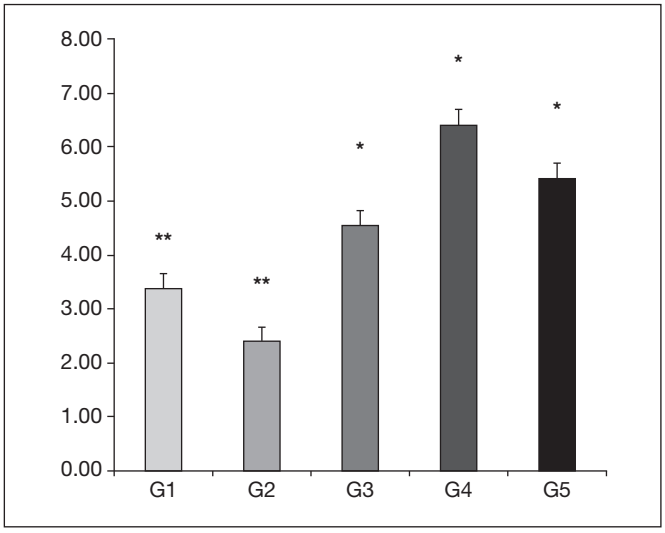

Figure 1. Student's *t*-test did not show a significant difference when comparing G1** with G2** (p=0.3759), but with statistical significance when compared with G3*, G4 * and G5 * (p<0, 05).

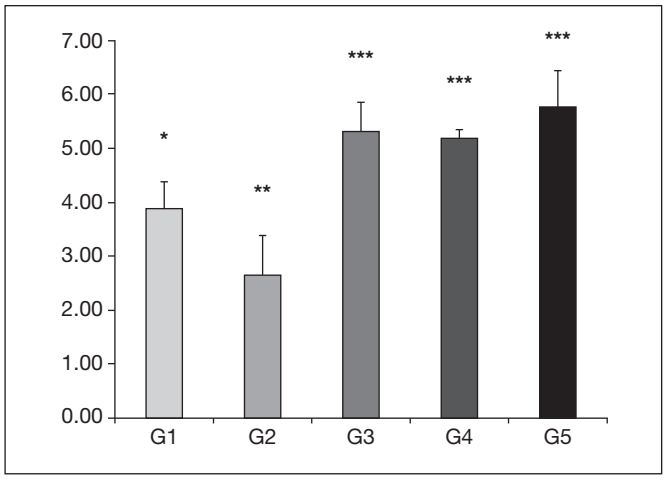

Figure 2. Student's *t*-test showed a significant difference when comparing G1* with G2** (p<0.05) and with G3***, G4*** and G5*** (p<0.01)

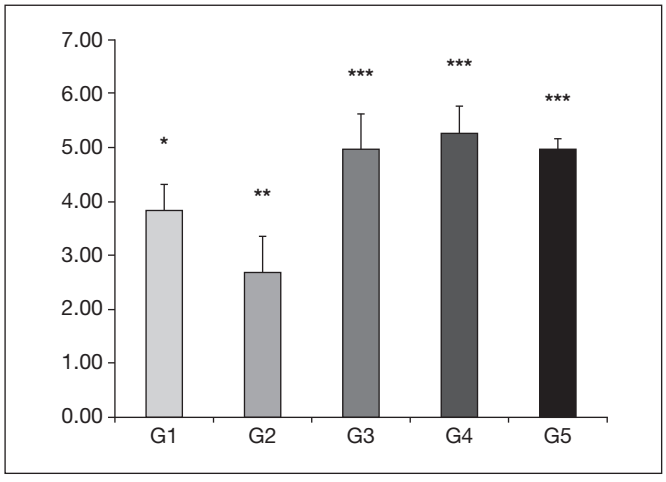

Figure 3. Student's *t*-test showed a significant difference when comparing the G1* with G2** (p<0.05) and with G3***, G4*** and G5*** (p<0.01)

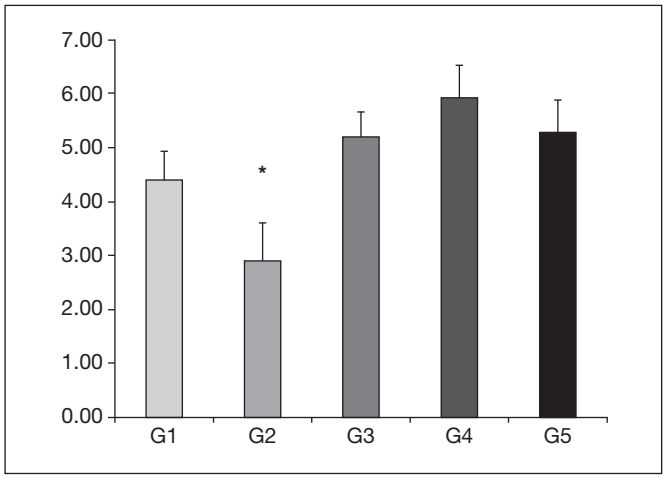

Figure 4. Student's *t*-test showed a significant difference when comparing G2* with groups G1, G3, G4, and G5 (p<0.05).

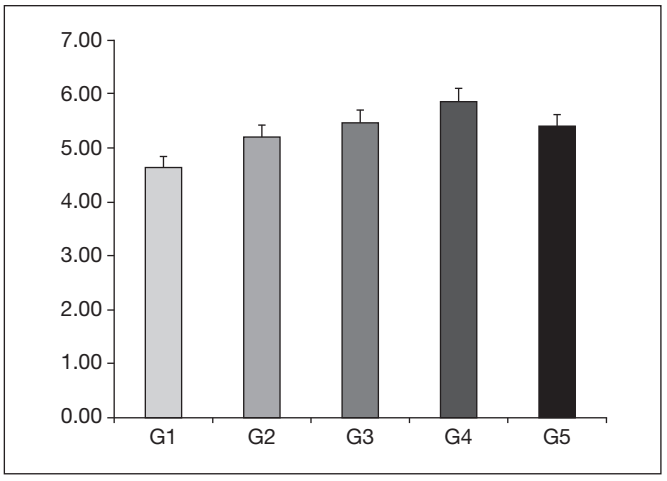

Figure 5. Student's *t*-test showed no significant differences between groups (p>0.05)

DISCUSSION

Opioids are important drugs for the treatment of pain. However, at the same time that they are initially analgesic and antihyperalgesic, they can later cause hyperalgesia, making the patient more sensitive to pain[2-5].

OIH has been attributed to acute desensitization of receptors by derailing G protein from opioid receptors, activation of NMDA receptors, among other mechanisms[2].

A study has shown that the concomitant use of low doses of opioid antagonists and NMDA receptor antagonists can prevent or reduce the development of OIH, and that ketamine in low doses can modulate OIH[7,22,23].

A review proves that the mechanisms involved in the development of OIH include the glutamatergic system and NMDA receptors, spinal cyclooxygenase activation, excitatory amino acids, dynorphins, cytokines, and chemokines, prostaglandins and downward facilitation. In this sense, it is speculated that the modulation of hyperalgesia can be done with NMDA receptor antagonists, alpha-2 adrenergic agonists, selective serotonin reuptake inhibitors, cyclooxygenase inhibitors, and GABA analogs[24].

In accordance with the present results, a study using fentanyl in Sprague-Dawuley rats caused OIH and demonstrated a mitigating effect by the drugs duloxetine and pregabalin[12].

In the present study, in the 2nd hour after the surgical procedure, there were no differences between the control groups, which received SS by IP associated with SS by gavage compared to the group that received fentanyl by IP associated with SS by gavage. However, when comparing these with animals that received duloxetine, fluoxetine, or pregabalin, it was found less hyperalgesia, demonstrating possible involvement of serotonin and norepinephrine receptors and reduction of calcium-dependent pro-nociceptive neurotransmitters in spinal cord release, in agreement with other studies[25-27].

When the animals were evaluated on the 1st and 3rd day after the surgical procedure, the group that received fentanyl via IP showed a greater hyperalgesic effect and with a statistically significant diffe-

rence in relation to the control group, evidencing OIH. However, the group that received fentanyl via IP, in addition to showing a significant difference in relation to the control with SS, showed a difference in relation to the duloxetine, fluoxetine and pregabalin group, which were different from the control group that received SS, suggesting effectiveness in reducing OIH.

On the 5th day after the surgical procedure, the group that received fentanyl maintained a higher pain response when compared to the other groups. However, although G1, which received SS, showed less hyperalgesic effect compared to the fentanyl group, it did not show any difference in comparison to the groups that received duloxetine, fluoxetine or pregabalin, still showing the presence of OIH.

On the 7th day, there were no differences between the groups; that is, the possible residual effect of hyperalgesia induced by a single dose of fentanyl was not evident.

Studies using duloxetine and fluoxetine to combat pain in rodents support the results of this study that 5-HT and NE play a critical role in attenuating persistent pain mechanisms, presumably through descending modulatory pathways from pain and consequently in OIH[28- 30].

The use of pregabalin on nociceptive behavior and SC in a model of trigeminal pain in rats, attenuating mechanical allodynia and SC on the model of trigeminal pain confirms its clinical use in the treatment of pain and, although there are few studies with OIH, there is evidence that it can be useful in controlling this type of pain[31].

CONCLUSION

The present study showed evidence that fentanyl produces OIH and is likely to have a mitigating effect mediated by serotonin and norepinephrine and by calcium channel blockage by the drugs duloxetine, fluoxetine, and pregabalin.

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Health biopsychosocial aspects of students and collaborators of a higher education institution suffering from headache

Aspectos biopsicossociais da saúde de estudantes e funcionários de uma instituição de ensino superior portadores de cefaleia

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ABSTRACT

BACKGROUND AND OBJECTIVES: Headache is considered a common health condition in doctors' offices around the world. It is an unpleasant sensory experience that will be experienced by the individual at least once in their life, be it an adult or child. The main challenge is to make an accurate diagnosis due to the signs and symptoms that may be related to other diseases. Its etiology is multifactorial and is often related to the individual's biopsychosocial condition. Thus, headache results in significant physical and emotional impact on the patient. The objective of this study was to identify the biopsychosocial aspects of the health of students and employees with headache from a higher education institution in the city of Vila Velha/ES.

METHODS: This research was a cross-sectional analytical study conducted from March to May 2019. The convenience sample consisted of 51 individuals of both genders, aged between 18 and 59 years old, who reported headaches.

RESULTS: Fifty-one individuals (female=41 and male=10) participated in the study; most individuals were single (n=38, 74.5%) and had no children (n=40, 78.4%); 62.7% were students and 32.7% were employees. The average time since the perception of the symptom was 105±118.3 months. According to the visual analog scale, the total average pain was 6.6±1.8. The impact of headache was measured by the migraine deficiency assessment questionnaire which showed 52.9% of individuals with a severe impact. This result resembles sleep disorders (58.8%), confirming that the headache is debilitating in the population studied.

CONCLUSION: It was observed that female students had a higher prevalence of headache and that the most prevalent type of pain is migraine, with an impact on the overall functionality of individuals.

Keywords: Headache, Migraine disorders, Physical therapy specialty, Sleep.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A dor de cabeça é considerada uma condição de saúde comum em consultórios médicos em todo o mundo. É uma experiencia sensorial desagradável que será experimentada pelo indivíduo, pelo menos uma vez na vida, seja ele adulto ou criança. O principal desafio é realizar um diagnóstico preciso devido aos sinais e sintomas que podem estar relacionados a outras doenças. Sua etiologia é multifatorial e frequentemente está relacionada à condição biopsicossocial do indivíduo. Dessa forma, a cefaleia resulta em grande impacto físico e emocional no paciente. O objetivo deste estudo foi conhecer os aspectos biopsicossociais da saúde de estudantes e funcionários com dor de cabeça em uma instituição de ensino superior da cidade de Vila Velha/ES.

MÉTODOS: Trata-se de um estudo do tipo transversal analítico, realizado entre março e maio de 2019. A amostra foi de conveniência e composta por 51 indivíduos, de ambos os sexos, com idade entre 18 e 59 anos e que apresentassem relato de dor de cabeça.

RESULTADOS: Cinquenta e um indivíduos (feminino=41 e masculino=10) participaram do estudo; a maioria dos indivíduos era solteira (n=38, 74,5%) e não tinha filhos (n=40, 78,4%); 62,7% eram estudantes e 32,7% eram empregados. O tempo médio de percepção dos sintomas foi de 105±118,3 meses. De acordo com a escala analógica visual, a dor média total foi de 6,6±1,8. O impacto da dor de cabeça foi mensurado pelo questionário de avaliação da deficiência de enxaqueca que apresentou 52,9% dos indivíduos com um impacto grave. Esse resultado se assemelha aos distúrbios do sono (58,8%), confirmando que a dor de cabeça é debilitante na população estudada.

CONCLUSÃO: Observou-se que as mulheres estudantes apresentaram maior prevalência de cefaleia e que o tipo de dor mais prevalente é a enxaqueca, com impacto na funcionalidade geral dos indivíduos.

Descritores: Cefaleia, Fisioterapia, Sono, Transtornos de enxaqueca.

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INTRODUCTION

The evaluation by the biopsychosocial model considers that the human body is a complex organism, influenced by several factors. Under this conception, health and disease are dynamically balanced conditions and are determined by biological, psychological, and social variables, all in constant interaction. Diagnosis, prevention and treatment of diseases should consider the contributions of these three sets of variables. Thus, the best way to take care of people is to consider that the etiology of health conditions is always multifactorial[1].

Headache is commonly known as a disabling health condition since ancient times[2,3]. However, only in 1988, the International Headache Society (HIS) suggested, through the publication of the article "Classification and Diagnostic Criteria of Headache", guidelines for classifying and diagnosing headaches according to their etiology[4].

Headaches are referred to as primary when there is no attribution of a specific cause, for example, migraine type, tension-type headache (TTH), or trigeminal autonomic. They are considered secondary when associated with another disorder or the consequence of aggression to the organism, of general or neurological nature, such as trauma, tumors, excess drugs, among others[4,5].

Among the headache types, TTH and episodic migraine are the most prevalent in the world population. Despite affecting both genders, TTH predominance is higher in females, at working age, between 30 and 39 years-old[6].

The social impact of headache is associated with school and work absenteeism, as well as reduced productivity, both school and economic, in the affected population[7,8]. The personal implications of headache are directly related to changes in personality, lifestyle, constant physical and psychological stress. Also, personal factors such as education, financial condition, and marital status are described as capable of influencing the clinical presentation of this health condition[9-11].

The presence of headaches in college students is increasingly common, overcoming the headache presence in workers. In this population, it is assumed that there is an association between the presence of headache with factors such as student overload, stress, irritability, insomnia, and depression. In addition, headache can influence family relationships and cause dissatisfaction with the studies of the affected individuals[12,13].

According to the biopsychosocial model, as important as identifying the disease is knowing whether the individual can work, perform their daily activities at work, at school, or in other social areas. Thus, defining and measuring disabilities enables to design and monitor the impact of health or health-related interventions. To this end, the World Health Organization (WHO) has developed the WHO Disability Assessment Schedule (Whodas 2.0), which provides a standardized cross-cultural health and disability measurement model[14]. Whodas 2.0 provides a universal measurement system for the impact of any health condition on functionality but has not yet been used to assess headache in patients.

Thus, this study aimed at knowing the biopsychosocial health aspects of students and employees with headache from a university in the city of Vila Velha/ES.

METHODS

This is a cross-sectional analytical study. Students and employees of a higher education institution in the municipality of Vila Velha were invited to participate in the research. The project was publicized by the university's social media and banners posted around the campus. The inclusion criteria were any gender, aged between 18 and 59 years, studying or working at the university and with a headache report. The exclusion criteria were fibromyalgia, temporomandibular disorders, neurological disorders, cardiovascular disorders, neoplasia, pregnant women, or not meeting the defined ICDH-3β diagnostic criteria. Fifty-three individuals enrolled in the project, but only the 51 who met the inclusion criteria were included.

A questionnaire was used to evaluate sociodemographic variables, including issues classifying headache according to the criteria established by the Headache International Classification of the Brazilian Headache Society[4]. The visual analog scale (VAS) was used to classify the headache intensity at the evaluation moment, and the average headache pain in the last three months[15].

The Migraine Disability Assessment (MIDAS) questionnaire was applied to rate the disability caused by headache in relation to professional and social life. It has seven questions related to work, social, family, and leisure activities in the last three months, besides analyzing the intensity and frequency of headache episodes[16,17]. The impact of headache frequency on quality of life was assessed by the Headache Impact Test (HIT-6). This instrument has six items related to pain, social, psychological cognitive functioning and distress[18,19].

The McGill questionnaire, designed to provide qualitative pain measures that can be statistically analyzed[20], was used to characterize the sensory-discriminative, affective-motivational, cognitive, evaluative, and miscellaneous aspects of individuals with headache belonging to this research[21].

The health and disability assessment was performed using the WHO Disability Assessment Schedule generic questionnaire version 2.0, 12 items (Whodas), which has six domains: cognition, mobility, self-care, interpersonal relationships, life activities, and participation in the last 30 days[14]. Sleep quality was also assessed by the Pittsburgh Sleep Quality Index (PSQI) through 19 questions that addressed subjective sleep quality, the occurrence of disorders, latency, duration, sleep aid, and daily sleep dysfunction to keep awake while performing some activity[22].

The Institution's Ethics Committee approved this study under opinion No. 3,162,150 of 2019.

Statistical analysis

The results were shown in absolute and relative frequency, mean and standard deviation of the mean. After the Shapiro

Wilk's normality test, it was observed that the variables did not have a Gaussian distribution and, therefore, for the correlation analysis, the Spearman correlation coefficient was used. To identify the correlation strength between the variables analyzed, it was assumed that the values of 0.0-0.29 indicated a weak correlation, 0.30-0.59 a moderate one, 0.60 to 0.89 a strong one and 0.90 to 1.00 a very strong one. All statistical analyses were performed using the Prism Pad Graph 5.0 software (GraphPad Software Inc., California), and a value of $p \leq 0.05$ was considered statistically significant.

RESULTS

Fifty-one female participants (n=41, 80.4%) with a mean age of 28 years-old (minimum = 18 and maximum = 59) were evaluated. Most were single (n=38, 74.5%) and had no children (n=40, 78.4%), and the number of students outnumbered employees (n=32, 62.7%; n=19, 37.3%, respectively) (Table 1).

The specific characteristics related to pain and its interference in the daily lives of individuals are summarized in table 2. The average time of symptom perception was 105±118.3 months (minimum = 5 months and maximum = 432 months).

At the time of the interview, 29 subjects reported headaches, with a mean pain intensity of 4±1.8 by VAS. In the pain assessment of the last three months, the VAS mean was 6.6±1.8. Most individuals reported bilateral pain (n=28, 54.9%), stable in relation to the onset of pain perception (n=22, 43.1%), with several recurrences in the month (n=16, 31, 4%), worsening in the afternoon (n=19, 37.3%), and was mainly accompanied by photophobia symptom (n=37, 72.5%), stress in the workplace (n=33 , 63%) and at home (n=26, 51%). Most reported perfectionism (n=28, 54.9%).

Qualitatively, the pain was assessed using the McGill questionnaire through the sensory, affective, cognitive, and miscellaneous domains. The total pain index was 42.1±23.3, which means a moderate pain index. Their results are described in table 3. The overall functionality evaluated by Whodas is also presented in table 3.

Table 4 shows the results related to the disability, impact, and sleep quality degree of people with headache. Pain disability degree evaluation through MIDAS showed that most individuals (n=17, 33.3%) had no or minimal disability. This result was followed by 14 individuals (27.5%) with a severe disabi-

Table 1. Characteristics of research participants (n=51)

Variables	Absolute frequency	Relative frequency (%)
Gender		
Female	41	80.4
Male	10	19.6
Marital status		
Single	38	74.5
Married	12	23.5
Divorced	1	2.0
Occupation		
Employee	19	37.3
Student	32	62.7
Number of children		
0	40	78.4
1	7	13.7
2	3	5.9
4	1	2.0

Table 2. Pain characteristics and effect on daily life (n=51)

Variables		
Symptom perception (months) (Mean±SD)	105.0±118.3	
Current pain (Mean±SD)	2.3±2.4	
Pain in the last 3 months (Mean±SD)	6.6±1.8	
Pain location	Absolute frequency	Relative frequency (%)
Unilateral	23	45.1
Bilateral	28	54.9
Condition relationship		
Improves	12	23.5
Stable	22	43.1
Worsens	17	33.3
Symptom frequency		
Less than once a month	7	13.7
Once a month	6	11.8
Many times per month	16	31.4
Many times per week	15	29.4
Continuously	7	13.7
Worst moment		
When getting up	8	15.7
In the morning	6	11.8
In the afternoon	19	37.3
In the evening	16	31.4
When sleeping	1	2.0
All-day long	1	2.0
Present symptoms		
Photophobia	37	72.5
Nausea	25	49.0
Vomiting	3	5.9
Influence of pain in the daytime		
Stress at work	32	63
Stress at home	26	51.0
Perfectionist behavior	28	54.9
Reduced appetite	14	27.5
Little interest in normal daily activities	13	25.5
Psychiatric/psychological problems	22	43.1
Headache classification		
Tension-type headache	23	45.1
Migraine	28	54.9

Table 3. Qualitative aspects of pain and overall functionality assessment (n=51)

McGill	Mean ± SD	Results
Sensory-discriminative	16±7.1	Moderate
Affective-motivational	7.6±4.4	Moderate
Cognitive-evaluative	2.5±1.2	Moderate
Miscellaneous	4.1±2.8	Mild
Pain index (Total)	42.1±23.3	Moderate
Whodas		
Daily activities	3.80±1.56	Moderate
Cognitive	3.57±1.6	Moderate
Mobility	3.61±1.56	Moderate
Self-care	2.37±0.96	Mild
Interpersonal relationships	3.07±1.56	Moderate
Participation	4.0±1.81	Severe
Total	20.43±6.48	

Table 4. Disability, impact and sleep quality degree (n=51)

Instruments	Absolute frequency	Relative frequency (%)
Disability		
Minimum or none	17	33.3
Mild	10	19.6
Moderate	10	19.6
Severe	14	27.5
HIT-6		
Little impact	6	11.8
Some impact	10	19.6
Substantial impact	8	15.7
Severe impact	27	52.9
Sleep quality		
Good	1	1.9
Bad	20	39.2
Disorder	30	58.8

HIT-6 = Headache Impact Test.

lity. The impact assessed by HIT-6 shows a predominance of individuals with severe impact (n=27, 52.9%). Regarding the sleep quality evaluated by PSQI, 30 individuals (58.8%) had sleep disorders.

Table 5 shows the correlations between the functionality domains addressed by the Whodas instrument and the other variables. Age showed a low correlation (r: 0.290) with the interpersonal relationship domain and no correlation with the other domains. Females showed a moderate correlation only with the social participation domain (r: 0.414) and the frequency of the symptoms denotes moderate correlation with the interpersonal participation domain (r: 0.397). By correlating photophobia symptoms, a moderate correlation was found in daily activities (r: 0.352) and mobility (r: 0.386). The correlation between Whodas and the instruments that assess headache disability, headache impact on the quality of life, sleep quality and pain quality was also analyzed, and MIDAS and HIT-6 did not correlate with self-care domain, while Pittsburg and McGill did not correlate with any of the Whodas domains.

DISCUSSION

In this study, most individuals with headache had migraines and women are the most affected; in the student group, there was a similarity between the number of individuals with migraine and TTH.

The predominance of individuals with migraine in this study, especially in females, corroborates the findings of a study that evaluated the characteristics of 2000 patients with primary and secondary headache, with a higher incidence of migraine[23]. Other studies found, besides the prevalence of headache in women, a mean age between 25 and 55 years, similar to the results presented in this study[6,12]. In addition, it was observed in this research that the older the person, the lower the impairment of interpersonal relationships, which can be justified by maturity and life-long experience. The evaluated women presented greater impairment of social participation. It is suggested that the fact that women have more frequent

Table 5. Correlation between demographic, disability, headache impact, sleep quality, and pain variables with global functionality domains assessed by Whodas 2.0 (n=51)

	Activity	Cognitive	Mobility	Self-care	Relationship	Participation
Age	0.220	0.072	0.163	0.201	0.290*	0.0056
Gender	0.179	0.045	0.154	0.050	0.147	0.414*
Symptom frequency	0.254	0.117	0.179	0.250	0.204	0.397*
Psychological	0.195	0.265	0.176	0.306*	0.251	0.248
Photophobia	0.352*	0.178	0.386*	0.153	-0.050	0.237
Phonophobia	0.336*	0.111	0.202	0.146	0.054	0.285
MIDAS	0.536*	0.392*	0.552*	0.210	0.289*	0.571*
HIT-6	0.497*	0.295*	0.490*	0.195	0.383*	0.649*
PSQI	-0.271	0.135	0.088	0.084	0.007	0.030
McGill	0.198	0.139	0.187	0.150	0.098	0.230

HIT-6 = Headache Impact Test; PSQI = Pittsburgh Sleep Quality Index; MIDAS = Migraine Disability Assessment. Values shown in r (Spearman correlation); * $p < 0.05$

episodes of headache may have hormonal influence, especially in the menstrual period and stress[6,24,25].

Regarding students, there was an analogy between individuals with migraine and TTH, corroborating a study that included 119 students from a public university in São Paulo, indicating the onset or worsening of headache after university admission, resulting in a decrease in productivity of their student activities[26].

Regarding marital status, a study showed that married people are susceptible to more episodes of headache, which may be justified by occupational and family demands, added to daily stress[27]. However, this study found that single individuals, mostly students, had a higher rate of headache. This is related to local and individual biopsychosocial factors, student overload, dissatisfaction with school, stress, irritability, insomnia and depression[12,13].

Headaches may be accompanied by symptoms such as photophobia and/or phonophobia, nausea and/or vomiting, which may lead to self-observed disabilities in daily activities[4,28]. A prevalence of photophobia symptoms associated with impaired mobility was found. Also, photophobia and phonophobia showed a correlation in the impairment of daily activities.

Self-assessed pain intensity in the last three months, through VAS and McGill, presented a moderate pain index. Most reported pain at the time of assessment, being relatively low compared to the previous three months. A study of 90 women divided into two groups (TTH and control) collected a sample of participants' saliva that was used as an indirect marker in pain activity[29]. An increase in the salivary amylase level of the experimental group was observed, matching the results obtained with the McGill application. This fact proves that McGill is an effective subjective questionnaire to measure pain.

Headaches are among the ten most disabling diseases in the world[30]. The disability degree demonstrated in this research was assessed using the MIDAS questionnaire, which identified no or minimal pain disability in most participants over the past three months. However, an important number of individuals with severe disability were found; among them, most had migraines. The association of migraine with a higher degree of disability resembles a study that evaluated 198 college students with headache, where a more significant disability was observed in migraine patients when compared with patients with TTH[31].

This disability assessed by MIDAS refers to partial or complete changes in work, household and leisure activities[32]. Most individuals had significant changes related to presenteeism by reducing by half, or less than half, their activities due to headaches. In addition, the greater the disability and impact on individuals' lives, the greater the impairment of overall functionality. This result can be attributed to a cognitive decline during headache episodes. This decline is mainly due to a reduction in process and reading speed, verbal memory and learning in tasks that require attention[33,34]. Thus, there is a negative impact on the health of individuals and this may eventually impact the professional and health care sector economically[11].

The economic impact related to presenteeism is 2.6 times greater than the number of absences, especially in individuals with episodic and chronic migraine[35]. In this paper, the headache impact on social functioning was classified as severe for most individuals. Individual factors, such as changes in personality, lifestyle, constant physical and psychological stress, economic and marital situations, as well as educational level, may contribute to this result[11].

Although most individuals had sleep-related disorders, no association was found with the evaluated overall functionality. Contrary to the results found in this research, some authors state that insufficient sleep may be the cause of headache, which also negatively impacts individuals' daily activities[36,37]. A review analyzed the influence of poor sleep and its implications for public health and found that insufficient sleep contributes to the emergence of cardiorespiratory disorders, psychological disorders, diabetes mellitus, migraine, among others[38]. This scarcity of sleep results in changes in behavior in the academic and work environment, with the onset of intellectual, physical and emotional problems.

Whodas is an instrument developed by WHO to measure disability and inability, supporting the International Health Classification model, in a biopsychosocial context, in the cognition, mobility, self-care, interpersonal relationships, and life activities domains[39]. Although headache is a common comorbidity in the population, its repercussions on activities and social participation, so far, have not been described in the literature. There are no studies with the application of the Whodas instrument in headache patients, which makes this an unprecedented research.

Although patients reported moderate impairment of pain quality and sleep-related aspects, these variables did not correlate with overall functionality aspects assessed by Whodas 2.0. It is suggested that Whodas 2.0's domains, evaluated by the short 12-item questionnaire, could have prevented the discrimination of functionality aspects that would be related to these factors. On the other hand, the quality of pain and sleep are subjective and individual aspects, marked by psychological conditions that may vary with the individual's history. Thus, in a sample, the results can be quite variable, preventing a statistical correlation.

CONCLUSION

According to the results of this study, headache is a condition that intensifies as social attributions expand. Thus, far beyond the disease perspective, this work, in an unprecedented way, demonstrated that the evaluation of personal, social, and family factors is fundamental to understand the headache triggering, the influences on its duration and the potential factors that contribute to its complications.

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Effects of cold versus hot compress on pain in university students with primary dysmenorrhea

Efeitos da compressa fria versus quente sobre a dor em universitárias com dismenorreia primária

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ABSTRACT

BACKGROUND AND OBJECTIVES: Dysmenorrhea is the most common gynecological complaint among young women. Several therapeutic resources have been studied, aiming at reducing pain. The objective of this study was to identify the influence of cold or hot compresses on pain intensity and pressure pain tolerance thresholds in women with primary dysmenorrhea.
METHODS: A single-blind randomized clinical study involving 40 young women divided into two groups: hot compress or cold compress, applied for 20 minutes on the lower abdomen and lower back regions. Pressure pain tolerance thresholds were evaluated by algometry in the vastus medialis, gluteus maximus, lumbar paravertebral muscles and supraspinatus ligaments L4-L5 and L5-S1. Pain intensity was assessed by the visual analog scale.
RESULTS: No significant changes in pressure pain tolerance thresholds were observed immediately after the application of the compresses, nor 30 minutes later. The comparison of the variation in the effect of changes showed no differences between the intervention groups, either regarding the pressure pain tolerance thresholds or the visual analog scale. However, both groups had a significant reduction in the visual analog scale right after the application and 30 minutes after the end of the intervention. Nevertheless, right after the use of the compresses, as well as 30 minutes after its end, the group that received the cold compress had a more significant reduction in pain intensity (p=0.002 and p=0.004, respectively).
CONCLUSION: Cold or hot compresses did not produce changes in pressure pain tolerance thresholds. However, pain perception was lower after this treatment, especially in the group using cold compresses.

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Keywords: Dysmenorrhea, Pain measurement, Physical therapy modalities.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A dismenorreia é a queixa ginecológica mais comum em mulheres jovens, e diversos recursos terapêuticos visando a redução da dor vêm sendo testados. O objetivo deste estudo foi verificar a influência de compressas frias ou quentes sobre a intensidade da dor e o limiar de tolerância de dor à pressão em mulheres com dismenorreia primária.
MÉTODOS: Estudo clínico randomizado simples encoberto envolvendo 40 jovens divididas em dois grupos: compressa quente ou compressa fria, aplicadas por 20 minutos nas regiões do abdômen inferior e lombar. O limiar de tolerância de dor à pressão foi avaliado por algometria nos músculos vasto medial, glúteo máximo, paravertebrais lombares e ligamentos L4-L5 e L5-S1. A intensidade da dor foi avaliada pela escala analógica visual.
RESULTADOS: Não foram observadas alterações significantes imediatamente após a aplicação das compressas, nem tampouco 30 minutos após a aplicação no que concerne aos limiares de tolerância de dor à pressão. A comparação da variação do efeito das intervenções não revelou diferenças entre os grupos de intervenção, tanto em relação aos limiares de tolerância de dor à pressão, quanto em relação à escala analógica visual. Entretanto, ambos os grupos apresentaram redução significante na escala analógica visual logo após a aplicação e depois de 30 minutos do término em relação ao momento anterior à intervenção. Apesar disso, logo após a aplicação da compressa, bem como 30 minutos após o término, o grupo que usou compressa fria exibiu maior redução da intensidade da dor (p=0,002 e p=0,004, respectivamente).
CONCLUSÃO: Compressas frias ou quentes não provocaram alterações no limiar de tolerância de dor à pressão, porém, a percepção da dor foi menor após a aplicação do tratamento, especialmente no grupo que fez uso da compressa fria.

Descritores: Dismenorreia, Mensuração da dor, Modalidades de fisioterapia.

INTRODUCTION

Dysmenorrhea is considered the most common gynecological complaint by young women and affects approximately 60-80% of the female population. It is characterized by pain in the lower abdomen and may be accompanied by nausea, vomiting, headache, dizziness and fainting[1,2]. Around 8-18% of that population report intense discomfort, causing absenteeism in several daily activities while suffering pain[3].

Dysmenorrhea may be rated in relation to intensity as light, moderate or severe, and to etiology as primary or functional, and secondary or organic[1,4].

Some resources have been used for the treatment of dysmenorrhea. The use of medicinal plants seems to be effective for the treatment of that dysfunction[5]. Resources such as yoga, acupuncture and acupressure have also been used to treat menstrual pain[6,7]. It has already been shown that the combination of transcutaneous electrical nerve stimulation (TENS) and thermotherapy produces acute pain relief in women with moderate to severe primary dysmenorrhea[8]. Yet, the use of drugs also has efficacy in its treatment[9].

Among the physical therapy resources available for analgesia, thermotherapy is an option commonly used for the treatment of dysmenorrhea[10]. The application of cold or heat through compresses is a practical and low-cost resource in their treatment[10]. A study[11] compared groups of 10 participants who received cold or hot compress applied to the lower abdomen, one to two days before the menstrual period, and during the menstrual period. The authors found, through the visual analog scale (VAS) and the McGill Pain Questionnaire, that volunteers who received treatment with cold compress presented a higher satisfaction with the method and a more significant reduction of pain in comparison to those who used heat.

As there are still few studies about the use of non-pharmacological and low-cost resources to reduce the pain during the follicular period, studies are required in order to assess the effectiveness of the options available for that purpose[10].

The objective of this study was to investigate the influence of a single session of cold compresses versus hot compresses on pain intensity and pressure pain tolerance threshold (PPT) in women with primary dysmenorrhea.

METHODS

One hundred eleven university students enrolled in higher education in a private educational institution in the city of São Paulo were recruited through direct contact. They were all informed about the research and signed the Free and Informed Consent Term (FICT) prepared according to the recommendations set forth in Resolution 466 of the Brazilian National Health Council and the Declaration of Helsinki.

The inclusion criteria were age between 18 and 30 years, independent walking ability and presence of primary dysmenorrhea. Exclusion criteria were pregnant women, smokers, having children, a history of uterine diseases, and the use of hormonal contraceptives.

Volunteers underwent an individual assessment in a private place for the collection of demographics, age, gender, ethnicity, education, weight, height and pain intensity.

Pain intensity was assessed by VAS[12]. It is a straight line from 0 to 10 cm drawn on a paper, where on one end is written "no pain" (point zero) and on the other end is "maximum pain" (point 10). Each participant was asked to score on the straight line her level of discomfort. The closer the mark was to the source (zero cm), the lower would be the intensity of pain perception. On the other hand, the closer to the end of the line (10 cm), the higher would be the pain intensity.

Sixty-five women with a history of primary dysmenorrhea and pain by VAS above 4 in the follicular phase were selected to participate in the study. Nevertheless, 15 did not express interest in participating; four were taking drugs, and six gave up participating before the assessment. The final sample consisted of 40 women, randomly divided by a simple draw in two groups: hot compress (HC-n=22) or cold compress (CC-n=18).

Participants were also assessed regarding PPT, which measures the pressure the person supports at a particular body site through algometry. The Wagner Force Dial (FDK/FDN SERIES Push Pull Force Gaga, GREENWICH CT, USA) algometer was used for it. The handheld device contains a 1cm diameter rubber end. The pressure was applied at a constant velocity of 1kg/sec until the volunteer reported the level of pain or discomfort. The reading is expressed in kg/cm^2. During the assessment, the volunteer was instructed to say "stop" as soon as the feeling of pressure changed from unpleasant to painful. The test was interrupted as soon as the volunteer indicated the onset of pain, and the final amount of force applied was recorded. Algometry was applied in six predefined muscle points, identified below, to assess PPT:

RLP: right lumbar paravertebral region, LLP: left lumbar paravertebral region. In that assessment, the subject remained in the prone position, with lower limbs extended[13].

SL: supraspinatus ligament L4-L5, L5-S1. The subject remained in lateral decubitus position, with lower limbs extended[14].

RMG: right middle gluteus; LMG: left middle gluteus. For that assessment, the subject remained in lateral decubitus position, with lower limbs extended, as previously described in literature[14].

Volunteers were assessed for VAS and PPT before, immediately after application of the compress and 30 minutes after its end.

Participants were instructed about the study procedures: they should be menstruating, they should not have taken, or taking drugs or any other method of pain relief and wear comfortable clothing at the time of the intervention.

Both groups received the applications on the day when they mentioned higher pain peak. The compresses were placed in the lower abdomen and lower back region for 20 minutes. The volunteer was positioned in lateral decubitus position, and a thin cloth was placed on the application sites in order to avoid burns and improve the fixation of the compresses on the site. The hot bags were made of synthetic rubber and heated with boiling water in an electric kettle. The cold bags were made of plastic containing cellulose-based gel and were kept in the freezer and removed at the time of application.

The Research Ethics Committee of Centro Universitário Adventista de São Paulo (UNASP-SP) approved this study under opinion number 2.141.655, 2017.

Statistical analysis

The data were analyzed by the SPSS v.24 statistical package for Windows and expressed as means and standard deviations. The demographic data were analyzed with descriptive statistics

and the Student's t-test performed the comparison between the groups for independent samples. The comparison of the interventions was made by the two-way Analysis of Variance (ANOVA) and to compare the change in the effect of the interventions (delta). The Student's t-test was used for independent samples. The α significance level established in all cases was 5%.

RESULTS

Table 1 shows the patients' demographics. The groups happened to be homogeneous with regards to age, weight, height, body mass index (BMI), temperature and perception of pain in VAS. Regarding algometry, no significant changes were observed immediately after the application of the treatments, nor even thirty minutes after the application has finished (Table 2).

The comparison of the effect variation of the interventions (delta between the moments immediately after and before, and between 30 minutes after and before) revealed no significant differences between the two intervention groups, both in relation to thresholds of pressure pain tolerance and as regards to pain perception.

Regarding pain intensity (VAS), both groups presented a decrease in that variable immediately after application and after 30 minutes of its end in relation to the moment before the intervention. Such differences were statistically significant (Table 3). The comparison between the groups in each of the three-time points assessed showed that there was no difference between them regarding pain perception assessed by VAS before the intervention (p=0.17). However, both after and 30 minutes after the intervention, the CG showed a more significant reduction of pain perception than HC (p=0.002 and p=0.004, respectively).

Table 1. Demographics data

Variables	HC (n=22)	CC (n=18)	p-value
Age (years)	20.91±2.24	21.06±2.10	0.834
Weight (kg)	58.62±9.39	61.73±16.21	0.478
Height (m)	1.61±0.09	1.62±0.06	0.769
Body mass index (kg)	22.61±3.86	23.41±5.57	0.609
Temperature (ºC)	35.77±0.54	35.75±0.53	0.916
Visual analogue scale (cm)	6.27±1.77	5.72±1.98	0.354

Data presented as mean±standard deviation. HC = hot compress group; CC = cold compress group.

Table 3. Evolution of pain intensity

Visual analog scale	HC (n=22)	CC (n=18)
Before	6.27±1.76*	5.71±1.98**
After	4.23±1.80	2.59±1.36
After 30 min.	3.53±2.37	1.70±1.36

Data expressed as mean ± standard deviation; HC = hot compress group; CC = cold compress group; *p<0.001 in the comparisons between before and after and between before and 30 minutes after the intervention with hot compress; **p<0.003 in the comparisons between before and after, between before and after 30 min after and between after and 30 min after the intervention with cold compress.

DISCUSSION

This study is similar to the survey[11] in which the efficacy of heat and cold in the treatment of primary dysmenorrhea was observed. The authors included 20 women, divided into two groups: group A consisting of 10 volunteers treated with a heated thermal gel bag, and group B, also consisting of 10 volunteers treated with cold thermal gel bag chilled in the freezer. Both techniques were applied for 20 minutes in the lower abdomen region, one to two days before the onset of menstruation. In this study, the application of the compress was similar to the one in the study mentioned above regarding time length and site of application of the compresses, but it differs in the amount of the sessions. Such authors performed three sessions, one to two days before the beginning of menstruation, and found that cold compress is more effective than a hot one for relieving menstrual pain.

The study assessed volunteers by VAS and also assessed pain by direct measurement, algometry. However, only through VAS it was possible to observe a significant improvement, as already shown by other authors[11]. And data corroborate these authors[11] in that cold compress is more effective than hot compress to relieve menstrual pain. Another study[15] showed that the effect of the application of ice on the skin has a direct action on neurons and pain receptors, lowering the speed and the number of nerve impulses. The speed of that effect is due to its action on the gate control of pain mechanism, leading to the release of endorphins and enkephalins, pain-relieving substances.

However, although cold has shown better results concerning the HC group, the latter also obtained benefits in terms of decreased perception of pain intensity. This decrease probably occurred because heat can reduce muscle tension, which would briefly give the sensation of pain reduction, and it

Table 2. Thresholds of pressure pain tolerance before, after and 30 minutes after the interventions

	HC			CC			
	Before	After	30 min	Before	After	30 min	p-value
RMG	4.77 ± 2.48	4.01 ± 2.22	4.09 ± 2.02	4.60 ± 1.64	4.25 ± 1.85	4.35 ± 1.72	NS
LMG	4.66 ± 2.32	4.25 ± 1.88	4.23 ± 1.68	4.74 ± 1.57	4.66 ± 1.62	4.47 ± 1.67	NS
PLD	3.45 ± 1.67	3.61 ± 1.58	3.58 ± 1.42	3.88 ± 1.70	3.66 ± 1.45	3.67 ± 1.31	NS
LLP	3.67 ± 1.57	3.63 ± 1.76	3.71 ± 1.44	3.85 ± 1.71	3.56 ± 1.30	3.83 ± 1.24	NS
SL L4-L5	3.61 ± 1.83	3.71 ± 1.75	3.52 ± 1.43	3.84 ± 1.26	3.65 ± 1.40	3.49 ± 1.24	NS
SL L5-S1	3.55 ± 1.70	3.56 ± 1.74	3.56 ± 1.54	3.58 ± 1.33	3.40 ± 1.23	3.56 ± 1.19	NS

Values in kg/cm², expressed as mean ± standard deviation. HC = hot compress group; CC = cold compress group. RMG = right middle gluteus; LMG: left middle gluteus; RLP = right lumbar paravertebral region; LLP = left lumbar paravertebral region; SL = supraspinal ligament; L4-S1, - L = lumbar; S = sacral; NS = not significant.

also acts on pain control by means of the gate theory, similarly to TENS, or even changing central pain thresholds or through a well-being sensation[16]. By conducting a review of physical therapy treatments in dysmenorrhea, a study[10] pointed out that thermotherapy, either by cold or heat, is a recurring treatment for that dysfunction. The authors added that both could eliminate or reduce pain in a practical and economical way.

Also, to demonstrate the effectiveness of therapeutic means as a treatment, a study[17] estimated the prevalence of primary dysmenorrhea in schoolchildren and compared the impact of exercise and hot water bag in the occurrence and severity of symptoms. The study concluded that both exercises and hot water bags led to a significant improvement in the severity of pain and menstrual distress in the groups studied. Subjects in both groups showed a clear change from moderate and severe degrees to a mild degree of pain. Although the change was evident after the first month of intervention, it became more prominent at the end of the third month in both groups.

Regarding non-pharmacological treatment options for dysmenorrhea, a study reports that interventions such as behavioral therapy, use of medicinal herbs, cutaneous electrostimulation, topical heat use, among others, have been poorly studied yet and lack good quality studies to confirm or not the effectiveness of such resources[18]. Such a statement is in line with a systematic review and meta-analysis reporting that although heat has been used for the treatment of dysmenorrhea, strict quality studies should be conducted in order to provide more robust evidence about that resource[19].

In this study, VAS and algometry were used to investigate the behavior of acute pain. Probably, no significant changes regarding algometry have been observed after both interventions since the time was short to promote changes in PPT, or it is even possible that the non-significance concerning PPT was due to the performance of a single compress session at the critical moment of pain.

This study has some limitations, such as the lack of a control group. There was also no specific test to confirm the occurrence of dysmenorrhea. Since the perception of pain intensity is a subjective measure, the data related to this variable were collected by self-report of the participants. Also, as pain may have a multifactorial etiology, the homogenization of women concerning the level of physical activity, lifestyle, and variables of emotional origin would possibly provide new information on that matter.

A strength of this study lies in the fact that assessments were performed by the same examiner, who was unaware of the treatment the volunteer had received. The application of the compresses was performed by a properly trained professional who was used to that kind of care, and the application of compresses was monitored individually to avoid differences in the length of time or form of application among the volunteers.

CONCLUSION

The application of cold or hot compresses caused no changes in the pressure-pain tolerance threshold in women with primary dysmenorrhea. Though, immediately after the application of compresses and 30 minutes after the end of the intervention, both groups presented a reduction of discomfort caused by pain. However, the CC group had a more significant reduction in pain intensity in comparison to the group that used HC.

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Pain threshold between men and women with different fat masses and percentages

Limiar de dor entre homens e mulheres com diferentes massas e percentuais de gordura

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ABSTRACT

BACKGROUND AND OBJECTIVES: There is a data gap regarding cold pain and pressure pain in healthy young individuals. The present study aimed to compare cold pain threshold and intensity and pressure threshold in young men and women with different fat percentages.

METHODS: The study included 30 men and 42 women aged between 18 and 25 years, divided into two groups: normal - body mass index ≤24.9 and overweight - ≥25. Fat percentage was estimated by tetrapolar bioimpedance, pain-pressure threshold by pressure algometer, cold pain threshold was timed, and the intensity measured by the visual analog scale.

RESULTS: The intensity of pain caused by cold showed no significant difference between groups, as well as the cold pain threshold and the initial and final pain threshold. The same behavior happened within the men and women groups. When comparing the difference between genders, pressure pain and cold pain thresholds had significant differences. Pain intensity did not differ between genders.

CONCLUSION: Fat percentage did not affect the response time of cold pain and pressure pain thresholds and pain intensity in young adults. When considering gender, although the cold pain threshold in men was higher than in women, pain intensity was similar.

Keywords: Body mass index, Obesity, Pain measurement.

RESUMO

JUSTIFICATIVA E OBJETIVOS: Existe uma lacuna de dados com respeito à dor ao frio e pressão em indivíduos jovens saudáveis. O presente estudo teve como objetivo comparar o limiar e intensidade de dor ao frio, e limiar de pressão em homens e mulheres jovens, com diferentes percentuais de gordura.

MÉTODOS: Participaram do estudo 30 homens e 42 mulheres com idade entre 18 e 25 anos, divididos em dois grupos: normal – índice de massa corporal ≤24,9 e sobrepeso – ≥25. O percentual de gordura foi estimado pela bioimpedância tetrapolar; o limiar de dor à pressão por dolorímetro; o limiar de dor ao frio foi cronometrado e a intensidade mensurada pela escala analógica visual.

RESULTADOS: A intensidade da dor provocada pelo frio não apresentou diferença significativa entre os grupos, assim como o limiar de dor ao frio e o limiar de dor à pressão inicial e final. O mesmo comportamento ocorreu intragrupos para homens e para mulheres. Quando comparada a diferença entre os sexos, os limiares de dor à pressão e ao frio tiveram diferenças significativas. A intensidade da dor não apresentou diferenças entre os sexos.

CONCLUSÃO: O percentual de gordura não interferiu no tempo de resposta dos limiares de dor ao frio, pressão e intensidade da dor em adultos jovens. Quando considerado o sexo, embora o limiar de dor ao frio nos homens tenha sido maior que nas mulheres, a intensidade da dor foi semelhante.

Descritores: Índice de massa corporal, Mensuração da dor, Obesidade.

INTRODUCTION

Pain is a sign that has an essential protective function[1]. Studies suggest that gender, among other factors, affects the sensitivity response to pain, with women having greater pain experience when compared to men, especially with regard to thermal stimuli, and body composition, and lean mass influence the sensation of pain[2], and areas with excess subcutaneous fat are less sensitive to painful sensation[3]. There is some evidence that the high body mass index (BMI) is associated with higher pain thresholds[4].

The use of cold is a therapeutic modality that aims to reduce painful conditions and inflammatory processes, especially in acute and subacute injuries[5]. However, the use of cold is a validated and accepted way to assess pain[6,7], as well as the pressure pain threshold[8]. The present study aimed to compare the threshold and intensity of pain to cold and pressure in young men and women, with different percentages of fat.

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METHODS

This is an experimental and quantitative study. The population was chosen by convenience and in a non-probabilistic manner. The sample consisted of 72 university students of both genders. There were 30 men aged between 18 and 25 years (21.26±2.46 years), body mass between 57.2 and 106kg (77.85±13.46kg), height from 1.61 to 1.92m (1, 77±0.074m) and BMI between 18.5 and 30.1 (24.67±3.65) and 42 women aged between 18 and 25 years (21.1±1.8 years), body mass between 43 and 118,500kg (68.30±16.54kg), height from 1.56 to 1.78m (1.65±0.05 m) and BMI between 15.90 and 48.60 (24.87±6.34).

Participants were divided into two groups: normal group – BMI up to 24.9, consisting of 36 individuals, 15 men and 21 women, classified as underweight and normal weight, and the overweight group – BMI ≥25, who could be classified as overweight, pre-obese, obese grade I, obese grade II and obese grade III, according to the classification proposed by the World Health Organization (WHO). The inclusion criteria were the absence of systemic diseases, musculoskeletal and skin lesions, chronic or acute in the last six months, and a history of hypersensitivity to cold.

Before starting the evaluation, the cold sensitivity test was performed with the ice cube, at a temperature between 0 ° and 4 °C, placed on the inner face of the forearm for up to 20 minutes. Five minutes after the removal of the stimulus, the appearance of a papula was considered positive, and individuals in whom the test was positive were excluded.

Each appraiser always performed the same function at all times of the assessment, and all measurements were taken on the same day, in the morning. Each individual went through four conditions: A, B, C, and D.

Condition A consisted of estimating the percentage of fat (%F) by tetrapolar bioimpedance (BIA), with equipment Body fat analyzer, model BF-906 (Maltron), being described as evaluation 1 (AV1) and was registered accordingly. The anthropometric data of each individual, height in centimeters and weight in kilos, were measured at the time of the exam and entered in the BIA, as well as gender, age and the level of physical activity performed. The collection of BIA was carried out as recommended by the Brazilian Association of Nutrology and the Brazilian Society of Parenteral and Enteral Nutrition. The individuals were instructed to discontinue the use of diuretics for at least 24 hours before the test, avoid the consumption of food and drinks up to 4 hours before the test, the practice of physical exercises until 8 hours before and the use of drugs that cause water retention. The examination was carried out with the individual at rest, removing all metal objects attached to the body, such as rings, earrings, bracelets, and chains.

The individual was placed in the supine position, barefoot and with the lower limbs apart, with the feet about 30cm apart from each other and with the upper limbs positioned along the body, remaining in this position for at least 10 minutes before the exam. It was performed the antisepsis of the electrode contact points with cotton soaked in 70% alcohol, and a pair of electrodes was placed on the right foot, a distal electrode at the base of the third and fourth toes and the proximal between the medial and lateral malleolus, with a distance of about 5cm between them. The other pair of electrodes was placed in the right hand, with the distal electrode at the base of the third and fourth fingers, and the proximal electrode close to the ulnar styloid process, also at a distance of 5cm.

In condition B, participants underwent pressure pain assessment, being instructed to report the moment when they felt pain when subjected to progressive pressure. The instrument used was the Kratos® algometer, capable of producing a pressure of up to 50Kgf. The pressure was applied to the internal region of the dominant thigh, 30cm above the tibiofemoral joint. The strength in kilogram-force (Kgf) necessary to cause the painful stimulus was described as evaluation 2 (AV2).

Then condition C was performed, in which the cold pain threshold in the internal region of the dominant thigh was evaluated, 30cm above the tibiofemoral joint**,** by applying 1kg of crushed ice packaged in a plastic bag, and the time was clocked to the pain threshold (evaluation 3 – AV3). After that, the individual pointed out the pain intensity using the visual analog scale (VAS). This procedure was described as evaluation 4 (AV4). A scale of the Techline Digital Bal 150pa brand was used to assure the exact weight of the crushed ice.

In condition D, condition B was reapplied, and the data obtained in this last stage were recorded as evaluation 5 (AV5).

The Research Ethics Committee of the Universidade Estadual do Oeste do Paraná – UNIOESTE approved this study, under opinion No. 2.588.581, with the prior signature of the Free and Informed Consent Term (FICT).

Statistical analysis

The results were tabulated in the software Excel 15.0 (Microsoft®), and, for the calculations, it was used the software Bioestat 5.0. The data were assessed for normality by the Kolmogorov-Smirnov test, presented as means and standard deviations, compared between groups by the unpaired t-test, intra-group paired t-test and the Mann-Whitney test for discrete variables. The accepted level of significance was 5%.

RESULTS

The characterization of the studied sample is shown in table 1. All variables studied showed normal distribution. Regarding height, normal BMI and overweight BMI groups showed no statistically significant difference (p=0.240). There was a higher statistically significant difference in the overweight BMI group, body mass, BMI (p<0.0001), and age (p=0.0032).

Regarding the variables of body composition analyzed by BIA, all had significant differences between the groups normal BMI (BMI up to 24.9) and overweight BMI (BMI≥25), the variables: body fat (%, kg), BMI, lean mass (%) and water (%) - (p<0.0001), resting basal metabolism (p=0.016), lean mass (kg) - (p=0.0006) and water (L) - (p=0.0005).

When compared between genders, except for BMI, there was no significant difference (p=0.424) (Table 2).

The intensity of pain caused by cold measured by VAS did not show any significant difference between the normal and overweight BMI groups (p=0.169). In the comparison between the

two groups, the cold pain threshold also had no statistically significant difference (p=0.258). The same behavior happened with the pain threshold at initial pressure (p=0.299) and final pressure (p=0.107). After cooling the tissue, the difference in the percentage of fat did not influence the response time from the pain threshold to the final pressure (Table 3).

The same behavior occurred within groups. Men with pain thresholds at initial (7.633±3.156Kgf) and final (6.966±2.684Kgf) pressure with (p=0.065) and in women (0.928±0.866Kgf) and (0.881±0.861Kgf) with (p=0.299) respectively, although without statistical difference between them, (Table 4).

On the other hand, when the difference between genders is compared, all thresholds expressed in Kgf had significantly higher values in men. When analyzing the cold pain threshold, men presented (176.8±131.3 sec) and women markedly lower values (18.0±10.9 sec) and p <0.0001. In the analysis of the pressure pain threshold, it was found that both men and women had their final threshold decreased in relation to the initial one, that is, after cooling. Only the intensity of pain reached similar scores and without statistical significance between genders (Table 5).

Table 1. Characterization of the sample

Variables	BMI Groups	Mean and standard deviation	p-value
Age (years)	Normal Overweight	20.6±1.7 21.9±2.1	0,0032*
Body mass (kg)	Normal Overweight	60.5±9.6 84±11.79	<0.0001*
Height (m)	Normal Overweight	1.71±0.076 1.7±0.096	0.240 (ns)
Body mass index (kg/m^2)	Normal Overweight	20.47±2.31 29.11±3.81	<0.0001*

Groups normal BMI (up to 24.9) and overweight BMI (≥25); ns = not significant; *significant at the level of p<0.05.

Table 3. Comparison of the averages of time from pain threshold to cold, pain threshold to initial and final pressure in both groups

Variables	Groups	Mean and SD	p-value
Pain threshold to cold (seconds)	Normal	75.3±106	0.258 (ns)
	Overweight	93.1±125.1	
Pain threshold at initial pressure (Kgf)	Normal	3.929±3.871	0.299 (ns)
	Overweight	4.407±38.15	
Pain threshold at final pressure (Kgf)	Normal	3.291±2.996	0.107 (ns)
	Overweight	4.297±3.791	

Groups normal BMI (up to 24.9) and overweight BMI (≥25); ns = not significant.

Table 4. Comparison of means and standard deviation of pain threshold at initial and final pressure in both genders

Gender	Pain threshold at initial pressure (Kgf)	Pain threshold at final pressure (Kgf)	p-value
Male	7,633±3,156	6,966±2,684	0.065 (ns)
Female	0,928±0,866	0,881±0,861	0.299 (ns)

Paired t-test; ns = not significant.

Table 5. Comparison of means and standard deviation of pain threshold at initial and final pressure, pain threshold at cold and pain intensity (VAS between genders)

Variables	Gender	N	Mean and SD	P value
Pain threshold at initial pressure (Kgf)	F	42	0.928±0,866	<0.0001*
	M	30	7.633±3,156	
Pain threshold at final pressure (Kgf)	F	42	0.881±0,861	<0.0001*
	M	30	6.966±2.684	
Pain threshold at cold (s)	F	42	18±10.9	<0.0001*
	M	30	176.8±131.3	
Visual analogue scale (0-100mm)	F	42	4±2.2	0.47 (ns)
	M	30	4.1±1.8	

Unpaired t-test and Mann-Whitney; ns = not significant; *significant at 0.05.

Table 2. Comparison of body composition variables means - tetrapolar bioimpedance

	BMI	Mean and SD	p-value	Gender	Mean and SD	p-value
Body water (%)	Normal	16.89±5.14	<0.0001*	M	18.33±7.22	<0.0001*
	Overweight	30.44±9.68		F	26.76±10.81	
Body fat mass (kg)	Normal	10.24±3.7	<0.0001*	M	14.70±7.58	0.0341*
	Overweight	25.39±10.95		F	19.17±12.79	
Body mass index	Normal	20.47±2.31	<0.0001*	M	24.23±3.67	0.424 (ns)
	Overweight	29.08±3.83		F	24.43±6.36	
Basal metabolic rate (kg)	Normal	1590.1±212.3	0.016*	M	1884.9±167.7	<0.0001*
	Overweight	1726.4±306.7		F	1496.4±201.5	
Lean mass (kg)	Normal	50.27±8.48	0.0006*	M	62.17±8.42	<0.0001*
	Overweight	58.44±11.7		F	48.02±8.46	
Lean mass (%)	Normal	83.14±5.13	<0.0001*	M	80.70±7.26	0.0003*
	Overweight	70.09±10.83		F	72.79±11.58	
Body water (LT)	Normal	36.8±6.2	0.0005*	M	45.40±6.13	<0.0001*
	Overweight	43.16±9.87		F	35.36±8	
Body water (%)	Normal	60.87±3.73	<0.0001*	M	58.97±5.20	0.0005*
	Overweight	51.15±8.77		F	53.10±9.12	

* Significant at the level of significance p <0.05; ns = not significant.

DISCUSSION

The present study showed significant differences in the evaluation of pain stimuli to cold and pressure, between men and women, however, without differences regarding the percentage of fat. Several studies have addressed the differences in sensory levels in different populations, with comparisons between race[9], age group[9,10], fat level[1,] and gender[2]. However, national literature is still poor in this regard.

The evaluation of pain by thermal stimuli has been well described, both with hot and cold stimuli[11]. In the present research, it was used the technique of local application of ice in the inner region of the dominant thigh, which generated painful stimuli in all volunteers, with no differences regarding the intensity when comparing the different BMI, as well as between men and women, but men had a significantly higher threshold. Such findings are similar to those in the study[12], which analyzed the pain threshold to cold, pain intensity by VAS and cold pressure in 30 women and 30 men from Lebanese universities. There was no difference in pain intensity, but concerning the threshold, it was higher for men. Similarly, a study that evaluated cold tolerance in young men and women showed that men tolerated the stimulus for a longer time[13].

The present study showed results similar to the study[14], which compared the pain effects of cold in 117 young people, 55 men, and 62 women, by immersion of the dominant hand. The study showed that men had a higher threshold and tolerance to cold-induced pain than women, with no significant difference regarding pain intensity.

Women are more sensitive to the pain of a mechanical, ischemic, or cold nature[15], as well as higher sensitivity to pressure pain[16]. Corroborating these statements, considering that it is an objective and valid method[17], in the present study, the pressure pain threshold was higher in men than in women. Biological and psychosocial factors explain these differences, with women being more vulnerable to the development and maintenance of painful musculoskeletal disorders[18].

The present study did not show any significant difference according to the amount of fat, contradicting results that suggest a higher pain threshold in individuals with a greater amount of fat[1,3,4]. The result found, in a way, was surprising, because although women had a significantly higher percentage of fat than men, they had lower pain thresholds to cold and pressure. In this study, the sample consisted of young university students, since large discrepancies in age can induce conflicting results[9,11,19,20], requiring further studies with a larger sample and even in individuals of different age groups.

CONCLUSION

The percentage of fat did not affect the pain thresholds to cold and pressure, as well as the intensity of pain to cold in young adults. Regarding gender, the intensity of pain was similar. However, the pain threshold to cold and pressure was significantly higher in men.

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Musculoskeletal disorders in banana culture workers

Distúrbios osteomusculares em trabalhadores da bananicultura

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ABSTRACT

BACKGROUND AND OBJECTIVES: Work-related repetitive strain injury/musculoskeletal disorders affect numerous rural workers causing functional physical impairment. This study aimed to investigate the prevalence of work-related musculoskeletal disorders in banana culture workers.

METHODS: From a list of banana culture workers linked to the Family Strategy, a questionnaire was applied to obtain socio-demographic data, rural property, health and labor, and the Nordic Musculoskeletal Questionnaire. Data were statistically analyzed using the statistical software R Development Core Team*.

RESULTS: Thirty-six workers from ten rural properties participated in the study. The majority were male (94.4%), age group from 20 to 49 years (75.0%), most of them with incomplete primary education (50.0%). Regarding musculoskeletal disorders, the main regions affected were lumbar (63.9%), shoulders (47.2%) and knees (44.4%), with more than one region affected per worker. Regarding the work, tasks were described as painful and tiring including cutting, loading, fertilization, costal pulverization of pesticide, plowing and thinning.

CONCLUSION: There are risks of musculoskeletal disorders among banana workers with risks of leave of absence due to illness, which may lead to losses in daily activities. There is a need to deepen the theme to promote health at work.

Keywords: Agriculture, Musculoskeletal pain, Occupational health, Rural population health.

RESUMO

JUSTIFICATIVA E OBJETIVOS: As lesões por esforços repetitivos/distúrbios osteomusculares relacionados ao trabalho têm afetado inúmeros trabalhadores rurais, ocasionando comprometimentos funcionais. O objetivo deste estudo foi investigar a prevalência de distúrbios osteomusculares relacionados ao trabalho na bananicultura.

MÉTODOS: Foi obtida a listagem de trabalhadores vinculados à Estratégia da Família e foram aplicados um questionário para obter dados sociodemográficos, da propriedade rural, de saúde e trabalho; e o Questionário Nórdico de Sintomas Osteomusculares. Os dados foram analisados estatisticamente por meio do programa estatístico *R Development Core Team**.

RESULTADOS: Participaram da pesquisa 36 trabalhadores de 10 propriedades rurais, sendo a maioria do sexo masculino (94,4%), com faixa etária entre 20 e 49 anos (75,0%), e ensino fundamental incompleto (50,0%). Em relação aos distúrbios osteomusculares, as principais regiões acometidas foram: lombar (63,9%); ombros (47,2%) e joelhos (44,4%), havendo mais uma região acometida por trabalhador. No trabalho, foram relacionadas tarefas penosas/cansativas junto ao corte, carregamento, adubação, pulverização costal de agrotóxico, roçado e desbaste.

CONCLUSÃO: Há riscos de distúrbios osteomusculares entre os trabalhadores da bananicultura, com riscos de afastamento do trabalho e prejuízos em atividades cotidianas. Há necessidade de aprofundar o tema visando a promoção da saúde do trabalhador.

Descritores: Agricultura, Dor musculoesquelética, População do campo, Saúde do trabalhador.

INTRODUCTION

Work-related repetitive strain injuries/musculoskeletal disorders (RSI/WRMD) cover 53% of occupational illnesses recorded at European Union[1] and 26% at US[2], according to data of 2014 and 2015, leading a large part of individuals to sick leave. RSI/WRMD-related leaves in Brazil have high prevalence, representing around 12% of all benefits granted by the National Institute of Social Security (INSS) in 2017[3].

These conditions are caused by overuse of the musculoskeletal system and are directly related to the task demands, the physical and organizational work environments[4]. RSI/WRMD affects men and women in the productive phase of their lives, causing pain, suffering and functional disability, leading to work leave and disability retirement[5]. They are highlighted by the functional physical impairment in the individuals' lives, leading to changes in activities of daily living[4]. Among the risk factors are the

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workload, accelerated production demand, lack of rest breaks, evaluation and punishment modes for production control[4,5]. When chronic, RSI/WRMD causes sick leave for short and/or long periods[6]. There is a high prevalence of musculoskeletal disorders in agricultural workers, mainly affecting the lower back and upper limbs[7-10]. In banana farming, due to work demands, there are correlations between work and the presence of musculoskeletal disorders[11,12].

The purpose of this study was to investigate the prevalence of WRMD in banana farming in the region of Registro, state of São Paulo.

METHODS

This is a cross-sectional observational study with a descriptive approach, which was conducted with workers from rural properties in the municipality of Registro, located in Vale do Ribeira, in the state of São Paulo, from December 2018 to April 2019. A list of individuals linked to rural neighborhoods within the sanitary territory of Jardim São Paulo's Family Health Strategy (FHS) was obtained, and the workers were subsequently selected, having as inclusion criteria to work in banana farming for a minimum of three months, for the sake of working relationships. Exclusion criteria were working time in banana farming less than three months and the presence of WRMD before working in banana farming.

Visits were made to workplaces and/or homes, as well as telephone contacts, and the study proposal was presented to the owner and workers, and the invitation for voluntary participation was made. After the consent of the worker, the pre-drafted questionnaire was applied, in an individual interview, containing sociodemographic data, such as gender, marital status, schooling, family income; about the rural property: number of workers/rural property, size of rural property in hectares in general and in agricultural production; and about the work: type of work contract, working time in banana farming, presence of muscle fatigue, over-tiredness, and painful and tiring tasks; and the Nordic Musculoskeletal Questionnaire (NMQ), validated in Brazil[13]. In the application of this instrument, the individual reported the occurrence of musculoskeletal symptoms considering the last 12 months and seven days preceding the investigation, also reporting the occurrence of leave from daily activities in the previous year.

The study was approved by the Research Ethics Committee of the Federal University of São Paulo, under opinion No. 2,877,092 of September 5, 2018. The participants signed the Free and Informed Consent Form (FICT).

Statistical analysis

Collected data were analyzed using the *R Development Core Team*® statistical program.

RESULTS

Thirty-six individuals from 10 rural properties in the region attached to the FHS of Jardim São Paulo participated in the research, corresponding to 95% of the banana farming workers in the region, as two workers could not participate in the study. The municipality of Registro is responsible for over 60% of all banana production in the state of São Paulo[14], and Brazil is considered the largest consumer of "in natura" bananas and the fourth largest fruit producer in the world[15]. This corresponds to 7% of world production, being the largest banana exporter, with more than two-thirds of production exported to other countries[16].

Each rural property had, on average, four workers (SD=2.8), with 22.2 hectares of land (SD=7.5) devoted exclusively to banana farming. From the 10 participating rural properties, only three of them had other productions besides banana, such as the cultivation of pupunha palm heart and ornamental plants. Only two farms were family farming; the others were commercial farms with employers and employees.

Most individuals (94.4%) were male, cohabiting or married (86.1%), with one child (38.7%) and incomplete elementary education (50.0%). Most of them had a family income of 1 to 2 minimum wages (71.4%), and 33.3% had an informal employment contract. The average working time in the banana farming was 11.8 years, most of them between 1- and 5-years (30.6%).

The data obtained regarding musculoskeletal disorders are shown in table 1.

Table 1. Musculoskeletal disorders, divided by affected body regions, period and body segment that led to some work leave

Affected body regions	Last 12 months	Last 7 days	Work leave in the previous 12 months
Cervical	33.3%	30.8%	23.1%
Shoulders	47.2%	52.9%	23.5%
Elbows	13.9%	28.6%	0.0%
Fists and/or hands	38.9%	53.3%	28.6%
Thoracic	41.7%	50.0%	12.5%
Lumbar	63.9%	40.0%	16.7%
Hips and/or thighs	30.6%	50.0%	8.3%
Knees	44.4%	68.8%	31.3%
Ankles and/or feet	27.8%	60.0%	50.0%

Note: There was more than one body region affected by worker.

In the NMQ, the main regions affected were lumbar (63.9%), shoulders (47.2%), and knees (44.4%). Concerning the last seven days, there was a higher prevalence for the knees (68.8%), shoulders (52.9%), and ankles/feet (60.0%). Regarding the impairment to performing daily tasks as a result of musculoskeletal symptoms, there was evidence of work leaves due to involvement, especially of the ankles/feet (50.0%), knees (31.3%) and wrists/hands regions (28.6%). In addition, among the respondents, 38.9% reported muscle fatigue, 41.7% over-tiredness, and 86.1% complained of painful and/or tiring tasks at work in banana farming.

The main painful and tiring work tasks related to musculoskeletal disorders are shown in figure 1.

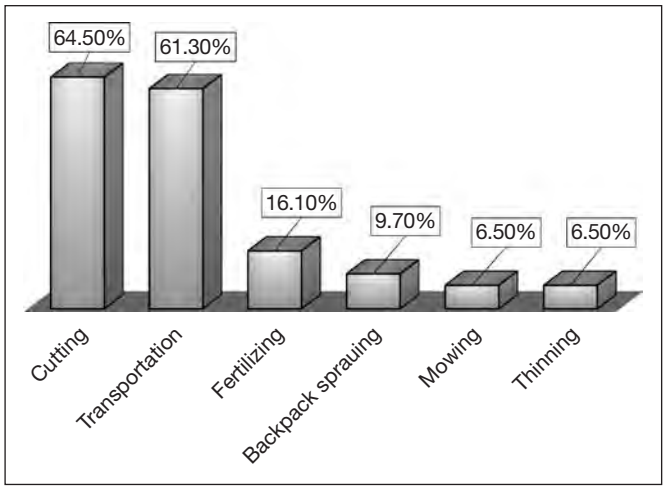

Figure 1. Main tasks considered painful and tiring in banana farming

The main tasks considered painful and tiring were cutting (64.5%), banana bunch transportation (61.3%) and fertilization (16.1%), in general, because they require inappropriate postures and repetitive movements. Also, 94.4% of the workers were employed and 5.5% were self-employed, but the production modes were very similar among them as regards the physical demands of the work.

DISCUSSION

The rural properties of the study are small, but they are important in the regional agricultural and economic production. Most of the rural banana farming workers in this study were male, aged between 20 and 49 years, with low schooling. According to preliminary data from the 2017 Agricultural Census, only 14% of rural workers in Brazil are literate, 43% had only elementary school and only 14% had concluded high school[17]. Regarding the employment contract, almost one-third of the workers had an informal employment contract. Informal work is a characteristic that is present in rural areas and is also related to low schooling[18,19]. The average time on the job in banana farming was 12 years. None of them reported working time for less than 12 months.

Rural workers have a much higher risk for musculoskeletal disorders in work activities compared to other occupations[8]. In this study, musculoskeletal disorders were predominant in the lumbar spine, shoulders and knees. The spine is the most affected region in rural workers, followed by the upper and lower limbs[9]. The lumbar spine is most affected mainly due to manual lifting and transportation of loads, as they perform repetitive movements with trunk flexions and rotations[20]. A relationship was also found between musculoskeletal disorders and work processes in fruit growing, with manual lifting and carrying of loads, sudden movements, exacerbated trunk flexion and biomechanical-postural misalignment[7,9,21-23].

In the tasks of cutting, transportation, fertilizing, backpack spraying, mowing, and thinning related to banana farming, there is a physical and repetitive movement requirement. Because the banana is a delicate fruit, the whole process of cultivation and harvesting requires great caution, demanding greater muscle strength and motor coordination of workers[11].

In the production of melon, tomatoes, walnuts, grapes and cotton, the presence of musculoskeletal disorders was evidenced mainly in the packing, weeding, harvesting, pruning and cutting tasks, and in the operation of agricultural machinery[9]. Repetitive activities using hand tools, lateral trunk flexion or inclination movements, squats, and working hours over 40 hours per week were also associated with a higher prevalence of chronic musculoskeletal pain[7,9,10,23].

In addition, over-tiredness and muscle fatigue were also reported by the study participants. Muscle fatigue and over-tiredness are usually associated with weight carrying, use of tools such as hoe and backpack pump for pesticide spraying as they are heavy[8]. Muscle can mean a warning condition for the body so that workers do not continue to perform the job function[24]. In banana farming, exposure to physical, chemical, biological, and ergonomic workloads was observed, as well as long working hours, the pressure to reach productivity goals, and low wages[12].

The study had limitations related to the sample size and because it was conducted in only one region that did not allow generalization for all banana farming workers. However, there are few studies related to banana farming work in Brazil and about the health of these workers.

CONCLUSION

Workers reported musculoskeletal disorders predominantly in the lower back, shoulders and knees. There were tasks considered painful and/or tiring, linked to cutting, transporting, fertilizing, spraying pesticides, mowing and thinning. There is a need for investigations and deepening aimed at the health of workers in banana farming.

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The management of pediatric pain and the perception of the nursing team in light of the Social Communication Model of Pain

O manejo da dor pediátrica e a percepção da equipe de enfermagem à luz do Modelo Sócio Comunicativo da Dor

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ABSTRACT

BACKGROUND AND OBJECTIVES: Pain is a multidimensional experience, and its management depends on both the professional's sensitivity and their ability to choose strategies for measurement and relief. The nursing team plays a fundamental role in this process since the assessment of pain in a systematic way provides the right therapeutic measures to the child. The present study aimed to evaluate pain and analgesia in the medical records and to understand the perception of the nursing team regarding the management of pain in hospitalized children.
METHODS: Qualitative, descriptive, exploratory research carried out in a tertiary level state university hospital. Data collection included patients hospitalized in a pediatric inpatient unit and a semi-structured interview with 24 members of the nursing team. A thematic analysis proposed by Minayo was used for data analysis. The analysis was performed following the Social Communication Model of Pain.
RESULTS: Eighty medical records were analyzed, and although pain is considered the fifth vital sign, most of the nurse prescriptions for pain remain blank in the medical records The participants' reports resulted in three categories: the naturalness of the pain in hospitalized children; the responsibility of the nursing team before the 5th vital sign; pain management.
CONCLUSION: Paying attention to the painful process of a child requires some skills from the professional to identify, assess, use proper instruments, understand the feelings involved in the process, and entail care in the prioritization of pediatric pain management.

Keywords: Nursing records, Pain, Pain measurement, Pediatric nursing.

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RESUMO

JUSTIFICATIVA E OBJETIVOS: A dor é uma experiência multidimensional e seu tratamento depende tanto da sensibilidade dos profissionais quanto de sua competência na escolha das estratégias para mensuração e alívio. A enfermagem possui papel fundamental nesse processo, sendo que a avaliação da dor, de maneira sistematizada, proporciona à criança medidas terapêuticas adequadas. O objetivo deste estudo foi analisar os registros sobre a avaliação da dor e analgesia nos prontuários e compreender a percepção da equipe de enfermagem quanto ao tratamento da dor da criança hospitalizada.
MÉTODOS: Pesquisa qualitativa, descritiva exploratória realizada em um hospital universitário estadual e de nível terciário. A coleta de dados contemplou prontuários de crianças hospitalizadas em unidade de internação pediátrica e entrevista semiestruturada individual com 24 membros da equipe de enfermagem. Para a análise dos dados, utilizou-se a análise temática proposta por Minayo. A análise foi realizada à luz do marco conceitual *Social Communication Model of Pain*.
RESULTADOS: Foram analisados 80 prontuários, e mesmo com a dor sendo considerada como quinto sinal vital, a maior parte dos registros da dor em prescrições de enfermagem permaneceu em branco. Os relatos das participantes resultaram em três categorias: naturalização da dor na criança hospitalizada; responsabilização da enfermagem diante do quinto sinal vital; manejo da dor.
CONCLUSÃO: Prestar o cuidado frente ao processo doloroso de uma criança exige habilidades do profissional para identificar, avaliar, utilizar instrumentos adequados, compreender sentimentos envolvidos no processo e significar o cuidado na priorização da assistência à dor pediátrica.

Descritores: Dor, Enfermagem pediátrica, Mensuração da dor, Registros de enfermagem.

INTRODUCTION

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage"[1]. Pain is always subjective, as each individual learns the application of the term through experiences related to previous injuries[2]. Even with advances in the scientific evidence on pediatric pain, children are still considered the most vulnerable group and exposed to painful experiences during hospitalization[3].

Since pain is a multidimensional phenomenon and considering the value of the complaint and its subjectivity in humanized care, pain was included as the 5th vital sign in order to alleviate suffering and ensure better patient care[4].

A child in pain may be exposed to the destabilization of other vital signs (SSVV), and the verification of pain as the 5th vital sign allows the identification of discomfort and instability signs. However, in most cases, it was observed that pain assessment and control are not yet incorporated into the nursing team's routine since only the classic verification of SSVV occurs in an institutionalized way[5].

Children have particularities in pain manifestation; therefore, professionals need to understand the stages of their development and the variations of age groups to be able to use assessment instruments and pain management strategies according to these particularities[6].

In addition, it is necessary to understand the specifics of multiple causal factors, in addition to tissue disease[7]. Considering this, pain is now understood as a distressing experience associated with real or potential injury to the tissue with sensory, emotional, cognitive, and social components[2].

Thus, it is only possible to understand the painful phenomenon of hospitalized children when we recognize that pain is subjective, i.e., each child experiences and expresses it individually. So, it is up to the person who is evaluating this pain to understand the meaning that the child attributes to his/her own pain in order to be able to perform appropriate management for each situation.

Based on these principles, bearing in mind that pain management is directed both to those who feel it and to those who assist, there are models that seek to understand the pain in its multidimensionality. One of these models, adopted as a conceptual framework for this research, is the Social Communication Model of Pain (SCMP)[8].

SCMP was developed aiming at understanding the pain episode integrating the biological, psychological, and social levels. The model is based on a linear time sequence of tissue injury or stress. Therefore, the pain experience may suffer inferences regarding the pain interpretation by those who feel it and by the person who can influence it[8].

Decisions about pain management are related to the professional's assessment of a situation and the role of the nursing team in pain management, which includes assessment, plan for pharmacological and non-pharmacological strategies, pain record and implementation, and evaluation of the patient's response to interventions[9].

Considering that pain management involves, from the moment of its identification in the nursing record, the multidimensional aspects of those who feel it and the professional who assists and the use of appropriate instruments for its evaluation, this study permeates the question of how the nursing team is perceiving the pain management of hospitalized children.

In this context, the objective was to analyze the nursing and medical teams' recordings regarding the assessment of pediatric pain and to identify the perception of the nursing team regarding the pain management of hospitalized children in the light of the Social Communication Model of Pain.

METHODS

Qualitative descriptive research based on SCMP. The research was carried out in a Pediatric Inpatient Unit (UIP) of a state, public, and tertiary-level university hospital in southern Brazil.

Data collection was carried out between 2016 and 2017, with information acquired in two stages: the first on the nursing and medical teams' recordings regarding the assessment of pain in hospitalized children and prescriptions of relief measures, contemplating, through an instrument developed by the researcher, the pain recording as the 5th vital sign; the pain recording in medical prescription and nursing notes; the prescribed analgesia and the analgesia performed by the nursing team.

The data from the first stage were collected retrospectively, referring to the period from August to October 2016, the selected period taking into account the highest occupancy rate of the unit in that year. Each medical record, regardless of the length of hospital stay, was analyzed for seven days or until hospital discharge.

The sample referring to medical records had as inclusion criteria the medical records of children who were hospitalized in the UIP for at least 48 hours; the presence of medical prescription; the presence of nursing notes. Medical records of children who died were excluded.

The sample resulted in 80 medical records and 360 medical prescriptions and nursing notes.

For data analysis, the Microsoft Office Excel® Software was used, in which a spreadsheet was created with the data, and inferences were made about them.

The second stage of data collection, based on the SCMP, included data on the characterization of participants and issues related to pain naturalization; pain recognition as a vital sign, knowledge regarding the evaluation scales, and the choice of measures for pain relief. The data were collected through interviews semi-structured by the chief researcher, with an individual approach in a private place with an average duration of 15 minutes, being captured by a digital recorder for later transcription in full.

The sample had as inclusion criteria having experience with pediatric nursing for at least one year, and those who were on vacation or leave during the collection period were excluded from the sample. The sample comprised 15 professionals from the nursing team, from different work shifts.

For data analysis, thematic analysis was used in which, after an exhaustive reading of the material, units of meaning and nuclei of meaning emerged, which meant something in relation to the analyzed object. The three stages of data analysis were followed: pre-analysis, material exploration, and treatment of the results obtained and interpretation[10].

After analyzing the data, three categories emerged: pain naturalization in hospitalized children, nursing accountability before the 5th vital sign, pain management.

The ethical precepts were followed when signing the Free and Informed Consent Term (FICT), and for reasons of secrecy and privacy, the names were replaced by the professional class abbreviation followed by a number, following an increasing order as the interviews were conducted.

The research project was submitted to the Human Research Ethics Committee of the State University of Londrina, based on resolution 510/2016 of the National Health Council (Brazil, 2016). It obtained favorable opinion No. 1.816.082, CAAE 61380316.5.0000.52.

RESULTS

The medical records analysis showed that 56% (n=45) of the hospitalized children in the selected period were male and 44% (n=35) female. Regarding the age, it varied between 29 days and five years old. The average length of hospital stay was five days, and the most prevalent diagnoses were: preterm newborns (PTNB) (n=16) and injuries and consequences from external causes (n = 11).
Regarding the nursing team records, it was found that 90% (n=324) had pain as zero or blank. From this number, 57% (n=205) had a pain episode record, and a drug was administered according to a medical prescription.
As for medical prescriptions, 60% (n=216) contained more than one analgesic option and it was found that 80% (n=288) included dipyrone, 75% (n=270) paracetamol, 25% (n=90) opioids (morphine and tramadol), 2% (n=7) ketamine and 2.7% (n=10) had no prescribed analgesia.

Pain management from the nursing team perspective
The participants worked for more than 10 years in the pediatric area, and the mean age was 46 years old. The report's analysis resulted in three categories: pain naturalization in hospitalized children, nursing accountability before the 5th vital sign, pain management.

Category 1 – Pain naturalization in hospitalized children
In this category, is expressed the personal experience of pain contemplated in the SCMP, the biological substrates for pain perception, the life history that can impact and determine the meaning and affective understanding of pain. The pain naturalization reflects the perception that each professional brings with them, their values and objectives, and may be associated with professional training and/or previous experiences that marked their path.
When asked about the pain presence during hospitalization, some professionals believed the fact that the child is hospitalized makes this natural, following the reasoning that if the child is hospitalized, he/she will consequently feel pain.

If he/she is hospitalized, it is because he/she has a health problem... he/she will probably experience some pain. He/she is already expected to feel pain. I think it's normal (AUX04).
As little as possible... but certain pains are beyond our control. We have nothing to do (TEC08).
I think so, depending on what he/she has, if this is cause for pain, it is normal for him/her to cry and feel pain. I have experienced this a lot with children, and I know it is normal (AUX02).

On the other hand, some participants reported that the hospitalized child should not experience pain because professionals must adopt measures, and the institution must provide what is necessary to relieve the child's pain.

No, there is no way he/she should be in pain. If he/she is in the hospital, he/she is not intended to feel pain. It is not normal to feel pain if it can be relieved. This is not what I believe in (TEC09).
I think it's like that, one concern we have is that the hospitalized child cannot feel pain. There is a child admitted to the hospital with all the infrastructure, and we cannot leave him/her in pain. At least, that's not how I learned (ENF04).

Category 2 – Nursing accountability before the 5th vital sign
In the second category, the relationship between the professional's perception before pain and extrinsic factors was observed, as proposed by the SCMP, i.e., the model recognizes complexity through multiple input sources, including not only expressive behaviors of the person in pain but also a range of contextual factors in which observers participate.
When asked about pain recognition as a vital sign, the reports demonstrated that pain assessment was not prioritized as the 5th vital sign, referring to work overload and other tasks as a priority.

Yes, I have been doing. I'll be very sincere. Lately, I have been insufficient because I'm very busy. You don't have time for anything, you have to take one here, and medicate the other there. Then automatically, as you saw the vital signs before, then you put zero. Because like this, I was in the infirmary, so for me, the most important thing is to medicate, run after the medication needed [...] one cries with pain, and then you change the bandage. Now that you asked, I realized I let it go unnoticed (AUX01).
I know that pain can be considered as a vital sign equal to temperature, heart rate, but when in a hurry with all the duties, I end up letting it go, and I only write it down when the child really cries in pain (TEC08).
Yes, inside the hospital, it is because it is like this, whenever we are asked, we take action, so I think so. And then I write it down in both prescriptions, sometimes I don't write in the back [space dedicated to the recording of vital signs], but in the front, I always write it down. I only write it down when he/she was in pain. We even know that we need to take notes at the time of the other signs, but there is a lot of demand here (AUX02).

Category 3 – Pain management
The third category is related to the intrinsic and extrinsic factors influencing the professional regarding the pain management proposed by the SCMP, and the model attributes to the management a complexity related to the experience of pain; the verbal and non-verbal variable; the physiological manifestations of pain; observers' reactions when they strive to assess and understand the child's pain; and the complex judgments associated with decisions to perform care or not.
The following reports referring to the pain's identification and relief demonstrate a sequence of perceptions, from the moment of observation of the painful phenomenon to the choice of the strategy to be used. It is observed that pain is not idealized as a vital sign, passing through the idea of recording only in moments of pain and ending with the choice of the pharmacological strategy as the only option.

I really assess the pain. I try, right? I look at the child, I think about what he/she may be feeling, I try to understand if it may be drama,

hunger, then when I see that it is not like that, I know it is a pain, right? I can tell when it is pain with the experience I already have, for so many years seeing children in pain (ENF03).
I write it down at the time of vital signs... because usually the child is calm and when he/she feels pain, then I write if the pain degree is one, two, three. But to tell you the truth, I do not always remember noting the pain, no, it goes unnoticed (AUX05).
I always do the simplest. If it is an uncomplicated child, if it is not written what it is, to begin with. Then if it is written, I do it as prescribed. For example, today, dipyrone and morphine were prescribed for the boy, then I start with dipyrone first (AUX03).

As for pain assessment, the SCMP emphasizes the relationship between training and education that the professional brings with him/her, standardized instruments in the institution, and the professional's perception. When asked about the instruments used, it was observed that professionals base pain assessments on their previous knowledge and perceptions.

I have used a scale like this; the child is tearful, uncomfortable. It's used more in small children, right? When he/she is older, he/she can speak to us himself/herself (TEC07).
As little babies, we can see by their behavior. When they move a lot, they twist, they get very restless. More because of their irritation. When they are in pain, have a fever, then everything is mixed up (TEC04).
Like this, with a bigger child, you ask, are you in little pain, in average pain or a lot of pain? Then you can evaluate more or less... Little pain is less than five; the average pain is about five; a lot of pain is considered 10 (ENF02).

The reports regarding interventions to relieve the child's pain permeated non-standardization and were exclusively pharmacological.

I start with the weakest. If there are morphine and dipyrone, I will make the dipyrone first. Then, if it doesn't provide relief, we do the strongest one (AUX08).
I start with paracetamol, then dipyrone, and, in the last case, morphine. Morphine is stronger, much stronger (TEC10).
If a child is not post-op, I start with dipyrone. If it is a child who is in the immediate postoperative period, I already think it has to be a dose of morphine or tramadol that is prescribed at medical discretion. Then you call the nurse and ask if you can do it or not. And if the doctor says no, then you give paracetamol. This is the criterion (TEC011).

DISCUSSION

The data obtained in this study indicated that even with the implantation of pain as the 5th vital sign since 2007, the nursing records related to pain assessment are still incomplete, and it was observed that there is no standardization of criteria for medical prescriptions elaboration. Besides, it was clear that professionals are aware of the importance of assessing pain in children. However, they use their own criteria and do not consider it as the 5th vital sign.

SCMP proposed by Craig[8] explains four sequenced steps, conceptually distinct, but interactive, after an initial painful event: (1) the child's pain experience, (2) the child's pain expression, (3) pain assessment by a caregiver, and (4) actions taken (or not) by others that would impact the child's pain.
Although pain is subjective, behavioral activity allows for observable inferences. Children's demonstrations of pain cause spontaneous reactions in observers, as well as the potential for empathy and clinical judgment[2].
The reports demonstrate that professionals naturalize pain during hospitalization, which does not make them cruel, but it corroborates the SCMP's statement that the professionals' beliefs directly interfere in the process of decoding pain.
Naturalizing or not pain goes beyond being empathetic, permeates acts, behaviors, beliefs, and attitudes of nursing professionals who need to be sensitive to the child's suffering and understand that they can react physically and emotionally to the painful process[11].
As evidenced in the reports, professionals start from their own conceptions for assessing pain and the expression of pain determines mainly, but not exclusively, the observer's assessment, and this reaction, in turn, will have an impact on pain management, depending on the reaction.
Among the factors that the observer will evaluate are the child's expressions and the component of the model that encompasses the child's expression and the caregiver's evaluation, which are the core and exemplifies the belief that pain is fundamentally a social experience[2].
Pain valuation by the professional and institution contemplates the situational context of interpersonal factors and the professional aspect of intrapersonal factors proposed by the SCMP. In the UIP of this study, pain was instituted as the 5th vital sign to incorporate the routine of the nursing team, since the presence of pain can trigger physiological changes in the child.
However, the reports demonstrated the prioritization of other tasks when assessing pain, corroborating the statement that nursing care focused on fulfilling duties leaves aside the meaning in nursing care from the perspective of showing zeal, attention, solicitude[12].
Thinking about the priority in care is to understand that the role of the nursing team goes beyond the painkillers' administration, it is the understanding of the pain multidimensionality of those who feel it and those who assist it. It is to redefine nursing care for children in pain to ensure their well-being, making hospitalization less traumatic[13].
Pediatric pain management includes pain recognition to the moment when the professional defines which strategies to use to relieve it. For this sequence of events to be carried out properly, the nursing professional needs to understand the importance of his/her role in this process and recognize how prepared he/she is to carry out this management[14].
This preparedness is evidenced in the SCMP as the professional training involved in the professional's intrapersonal factors, which in practice is illustrated as transmitted content, institutional training, and previous knowledge[8].
Adequate pain management begins with the assessment and understanding of problems taking into account the patient's uni-

queness. A study carried out with 261 nurses from three public hospitals showed that 88.8% believe it is important to assess and document pain, while 11.2% believe it is not important. However, 72% reported not carrying out the assessment using standardized protocols and scales and attributed this to the lack of training and previous experiences with hospitalized children[9].
Likewise, the UIP nursing team believes in the importance of pain assessment and documentation, but its practice is based on their own habits, beliefs, and attitudes to the detriment of available scientific knowledge and institutional standards.
A study carried out at the concerned UIP in 2015 observed that during the subsequent years, with the establishment of pain as a vital sign, training by professionals from the education center, and training by resident nurses to use the instruments was provided. However, professionals continue to justify not using it because they do not have knowledge[4].
Also related to the UIP, in 2011, a study analyzed 385 medical records of hospitalized children and found that 51.4% did not have their pain intensity quantified[16]. Likewise, a study carried out[3] in a Canadian hospital, found that in a UIP, within 24 hours, there was no documentation of pain assessment.
SCMP[8] refers to the pain assessment and recording step as the third sequential step of the four existing ones, conceptually distinct, but interactive, after an initial painful event. The proposed model states that by not performing a reliable assessment or recording it, it can influence the fourth step, which consists of taking action in the face of pain.
As in all process stages, judgments of caregivers and decisions to offer and provide care are mutually influential. The actions taken by a caregiver can also affect their assessment. Besides, how a caregiver manages a child's pain can also return to the beginning of the sequence and impact how a child's pain experience is created[17].
Faced with the actions that the professional decides to take and considering that the analgesia administration is the last step of the linear sequence proposed by the SCMP, medical prescriptions also play an important role, since professionals choose certain pharmacological therapies, and need to be adequate to the age group and diagnosis.
In the reports and medical prescriptions analyzed, there was a lack of standardization in the choice of drugs, both by the nursing team and by the medical team when prescribing analgesics.
In contrast to this finding, in the guidelines on the pharmacological treatment of pain in children, there was an update of the analgesic ladder, recommending the use of analgesic treatment in two steps, according to the degree of severity of the child's pain.
This strategy consists of choosing the category of analgesic drugs according to the level of pain intensity in the child: for children evaluated with mild pain, paracetamol and ibuprofen should be considered as first options; whereas those evaluated with moderate to severe pain, the administration of an opioid should be considered.
The World Health Organization also recommends the use of non-pharmacological strategies, in line with the SCMP, which states that the pediatric pain trigger event is often closely associated with fear, anxiety, and stress[17].
Among the most commonly used non-pharmacological measures, methods of distraction, relaxation and comfort can be mentioned; hot water bag, non-nutritive suction, affection, calming, recreational activities and informative conversation about pain.
However, it was evident in this study that the organizational culture associated with the lack of empowerment on the part of professionals leads to choices of exclusively pharmacological measures for the relief of pediatric pain.

CONCLUSION

Nursing professionals are sensitive to pain relief, but just offering training on pain assessment instruments, although important, is not enough to achieve continuity of care and alleviate the pain of hospitalized children.
The achievement of adequate pain management depends directly on the articulation between intrinsic and extrinsic factors of the one who feels the pain and of the one who assists it, according to the assumptions of the Social Communication Model of Pain.

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Central sensitization and beliefs among patients with chronic pain in a primary health care unit

Sensibilização central e crenças entre pacientes com dores crônicas em uma unidade de atenção primária de saúde

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ABSTRACT

BACKGROUND AND OBJECTIVES: The pain that persists for more than three months is classified as chronic pain. Current studies suggest the existence of a dynamic relationship between biological changes, psychological state, and social context within the pain phenomenon and its chronicity. Central sensitization can be defined as the amplification of the neural signaling within the central nervous system that causes pain hypersensitivity, characterized by overlapping symptoms. The objective of this study was to evaluate the central sensitization, dysfunctional beliefs and other variables such as self-perception about sleep quality in a group of patients with chronic pain.

METHODS: The patients answered sociodemographic questions, questions about pain-related habits and beliefs, and completed the central sensitization questionnaire.

RESULTS: The 30 participants involved in the study had a mean value of 49.86±16.14 for central sensitization, as well as a high presence of dysfunctional beliefs and poor sleep self-perception.

CONCLUSION: The need for a biopsychosocial look aiming to investigate the beliefs and level of central sensitization of patients with chronic pain is becoming increasingly necessary, as it is essential to understand the socioeconomic conditions of each individual for better evaluation and management. An initial educational approach in an easy language that stimulated the reflection and participation of patients to understand their symptoms was well accepted by these patients.

Keywords: Chronic pain, Health education, Pain management, Primary health care.

RESUMO

JUSTIFICATIVA E OBJETIVOS: É classificada como dor crônica a dor que persiste por um período superior a três meses. Estudos atuais sugerem a existência de uma relação dinâmica entre mudanças biológicas, estado psicológico e contexto social dentro do fenômeno da dor e de sua cronificação. A sensibilização central pode ser definida como a amplificação da sinalização neural dentro do sistema nervoso central que provoca hipersensibilidade à dor, caracterizada pela sobreposição de sintomas. O objetivo deste estudo foi avaliar a sensibilização central, crenças disfuncionais e outras variáveis como autopercepção sobre qualidade do sono em um grupo de pacientes com dores crônicas de uma unidade de atenção primária de saúde.

MÉTODOS: Os pacientes responderam a questões sociodemográficas, questões sobre hábitos e crenças relacionadas à dor e preencheram o questionário de sensibilização central.

RESULTADOS: Os 30 participantes incluídos no estudo apresentaram o valor médio de 49,86±16,14 para sensibilização central, além de elevada presença de crenças disfuncionais e autopercepção ruim do sono.

CONCLUSÃO: A necessidade de um olhar biopsicossocial, que se proponha a investigar as crenças e o nível de sensibilização central de pacientes com dores crônicas se mostra cada vez mais necessário, assim como é fundamental compreender as condições socioeconômicas de cada indivíduo para melhor avaliação e cuidado. Abordagem inicial educativa, com linguagem acessiva, que estimula a reflexão e participação dos pacientes para a compreensão dos seus sintomas foi bem aceita pelos pacientes.

Descritores: Atenção primária à saúde, Dor crônica, Educação em saúde, Manejo da dor.

INTRODUCTION

Pain that persists for a period longer than three months is classified as chronic pain (CP), and this definition is consistent with several widely used epidemiological references[1]. Current studies on CP suggest the existence of a dynamic relationship between biological changes, psychological status, and social context, emphasizing that these factors have different roles in CP, disability, and emotional maladjustment[2].

There is strong evidence that CP may be associated with physical disability, emotional disorders, and social difficulties. In addition, it has been recognized that emotional, cognitive, and social factors mediate the subjective experience of pain[3].

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Physical pain, whether acute or chronic, is often reported along with anxiety and depression disorders[4-6]. Systematic reviews and recent cross-sectional studies have concluded that the combination of a depressive disorder, or anxiety disorder, with pain, is associated with a worse clinical outcome and increased use of the health system and health care costs than when pain is presented in isolation[7,8].

According to the biopsychosocial model of pain[9], the manifestation and maintenance of CP are dynamic functions of predispositions, stimuli, and preceptor responses and maintaining factors, variables that may include genetic factors, learning processes, and occupational factors. Preceptor stimuli can be external and internal and involve stressors and values capable of triggering several autonomic and musculoskeletal responses (e.g., sympathetic activation and muscle tension). Such responses are mediated by the perception and interpretation of physiological processes or symptoms and may involve expectations, learning processes, and beliefs, as well as coping strategies. Maintaining variables can be influenced by learning processes and other psychosocial factors. According to this model, biological aspects can initiate, maintain or modulate physical changes; psychological factors influence the assessment and perception of physiological signs, and social factors shape the patient's behavioral responses to the perception of his/her physical changes[9,10].

Recent reviews have highlighted the contribution of sleep disorders to the experience of pain[11,12]. Several studies indicate that sleep deprivation leads to a series of complications to general health, such as hyperalgesic responses in humans[13] and impaired function of the endogenous pain inhibition systems[14].

Biopsychosocial treatment that recognizes and targets the physical, psychological, and social factors underlying pain and disability is currently accepted as the most effective approach for CP[15,16] and superior to the usual treatment and isolated physical therapy[17].

The presence of CP is often associated with the presence of other clinical symptoms, including fatigue, poor sleep, cognitive deficits, headaches, depression, and anxiety[18]. A study[19] proposed the term "central sensitivity syndrome" (CSS-CS) to categorize inorganic pain-related disorders with overlapping dimensions of symptoms, with central sensitization (CS) being the common etiology. CS has overlapping symptoms in a spectrum of structural disease, from those with persistent nociception, for example, osteoarthritis, and those without physical tissue injury, such as fibromyalgia and myofascial pain syndrome[20].

Non-pharmacological strategies with the primary objective of reducing health costs associated with pain treatment and concerning its cost-effectiveness seem to be a great option for the implementation of pain understanding programs. These programs focus on a biopsychosocial approach in a multiprofessional way, concluding that it can be more economical for the health system, in addition to providing a better quality of life for people with pain[21] compared to the unilateral use of conventional medicine[22].

This study aimed to assess the emotional and mental health aspects linked to CS, dysfunctional beliefs and habits related to the perpetuation of CP and self-perceived sleep. Besides developing and conducting a Pain Education class based on neuroscience with accessible language, in a group, encouraging patients to participate in understanding what pain is, and reconceptualizing their symptoms, investigating their acceptability.

METHODS

A descriptive cross-sectional study with a brief educational intervention was carried out with patients with CP from a Basic Health Unit located in the city of Guarulhos in the state of São Paulo.

In a first contact, patients filled out questionnaires that subjectively assessed the level of pain felt, the impact of pain on daily activities, CS, and the beliefs and knowledge related to the care of musculoskeletal pain, and questions regarding the use of alcohol, tobacco, self-perceived physical activity, and sleep quality. They were also asked about the number of drugs in use for pain control, counting the prescribed and non-prescribed drugs. Neurological patients, polytrauma patients, or those with major functional deficits were excluded.

The Pittsburgh Scale (PSQI-BR) translated and validated for the Brazilian population[23], was used to assess sleep quality during the last month, which consists of a questionnaire with 19 items, and the first four questions that assess, in the previous month, the time they usually went to sleep; the time in minutes that they typically take to fall asleep; the time they usually wake up; the number of hours of sleep; and self-assessment of sleep quality.

The Central Sensitization Questionnaire (BP-CSI) was used to assess the degree of CS. The questionnaire was validated and translated into Portuguese, and it consists of two parts. Part A contains 25 statements that can be scored on a Temporal Likert scale of 5 points, from zero to four. The higher the value, the greater the degree of CS, which can vary from zero to 100 points in total. Part B assesses whether the patient has previously been diagnosed with any of the diseases included in CS syndrome and the year of diagnosis. Given the condition of the population studied, and the difficult access to specialist doctors, part B of the questionnaire was not used. However, health diagnoses with signs of CS were ruled out during the class of biopsychosocial aspects of pain[24].

To assess the intensity of pain in the previous week, the Numeric Rating Scale (NRS), from zero to 10, was used, where zero represents "no pain," and 10 represents "the worst pain imaginable." Also, on scales from zero to 10, patients rated how much pain interfered with their self-care activities, household chores, and outdoor activities, and how much they avoid leaving the house due to pain.

To assess some dysfunctional beliefs related to pain, patients responded yes or no to questions such as: when the pain increases, do you believe that it is your body that is "hurting more"?; "Do you believe that stress or anxiety can increase your pain"?; "Do you believe that exercises or movements can make your pain worse"?; "Do you believe that radiography and magnetic resonance imaging tests define your condition"?

After the assessment, the patients met in groups for the expository-participatory class on the neurophysiological aspects of pain and psychosocial factors that are related to the chronicity of pain.

The class lasted 1 hour and 30 minutes, with spaces for free exposure and questioning of patients, and was constructed in an easy language, using metaphors and common examples of how emotions play a central role in the painful experience. The purpose of the class was to stimulate reflection and reconceptualization, recognizing dysfunctional behaviors and thoughts related to the painful phenomenon.

Explaining pain, or educating about pain, refers to a range of educational interventions that aim to change the understanding of multiple aspects of pain, based on evidence, so that understanding is a pain reduction mechanism, based on educational psychology, in conceptual change strategies, to help patients understand the biology of pain. Pain education is not behavioral or cognitive counseling, nor does it deny the potential contribution of peripheral nociceptive signals to the experience of pain[25].

The application of the biopsychosocial model has focused on the impact of pain on the patient and those around him/her. The importance of psychosocial factors as mediators of suffering has been recognized in the literature, and several treatments and approaches recognize pain education as an effective strategy to modulate the factors that determine the painful experience[25].

At the end of the application of the questionnaires and the class on biopsychosocial aspects of pain, patients also responded, on visual scales from zero to 10, regarding the satisfaction to participate in this class and the importance of the theme. If the need for psychological support was observed, the patient was referred to the psychological support team.

After the class, the patients were individually scheduled for consultations and guidance with physical therapists on the best care and elaboration of conduct.

The Research Ethics Committee of Universidade Nove de Julho approved this study under CAAE opinion: 04098618.1.0000.5511, conducted from March to May 2019.

RESULTS

Thirty patients were included, with a total of 8 groups, with a mean age of 55.5±12.32 years old, 22 women and eight men. The regions with the highest number of CP complaints were the lumbar spine, followed by the knee and shoulder. The duration of pain complaints was 50.96±46.83 months (Table 1).

Among life habits, 93.3% of patients consider themselves to be sedentary, 44.4% live close to smokers. Fifty percent consider sleep quality poor, 26.66% very poor, with an average hour of sleep of 5.75±1.99. Other values about life habits and self-perception of sleep quality are shown in table 2.

Table 3 presents the values related to the level of pain and impact on daily activities using the numerical estimate scale from zero to 10, where the values found, both for the level of recent pain and the level of pain in indoor and outdoor activities, were high. The average score found with the application of the CS questionnaire was 49.86±16.14. Table 4 shows the values for the items in the CSS questionnaire that had a higher average score among the participants.

The volunteers answered the questions about pain-related beliefs with yes or no. Table 5 shows the answers.

Table 1. Sample characteristics (n=30)

Variables	
Age (mean±SD)	54.5±12.32
Gender (men / women)	8/22
Number of children (mean±SD)	3.23±2.11
Family income in number of minimum wages (R$ 998.00) (mean±SD)	1.64±0.73
Number of chronic pain complaints by location	
''All over the body"	4
Head	1
Neck	2
Shoulder	6
Lumbar spine	15
Knee	8
Upper limb	3
Lower limb	1
Painful complaint time (mean ± SD)	50.96±46.83
Drugs in use for pain prescribed (mean±SD)	1.33±1.39
Drugs in use for pain not prescribed (mean±SD)	0.56±0.50

Table 2. Life habits and self-perception of sleep quality

	n (%)
Sedentary (do not perform physical activity)	28 (93.3)
Smokers	3 (10)
Live close to smokers	13 (44.4)
Drink alcoholic beverages	5 (16.6)
Sleep quality self-assessment	
Very good	3 (10)
Good	4 (13.33)
Bad	15 (50)
Too bad	8 (26.66)
Total hours of sleep (mean ± SD)	5.75±1.99

Table 3. Values related to the level of pain and impact on daily activities according to the numerical estimate scale from zero to 10

	Mean±SD
Pain level felt in the previous week	7.96±1.99
How much pain disrupts your self-care	7.36±2.47
How much pain disrupts household chores	7.43±2.66
How much pain disrupts outdoor activities	7.63±2.39
How much you avoid leaving home due to pain	7.93±3.03

Table 4. Items of the central sensitization inventory with the highest score presented

Overall average score (zero-100)	Mean ± SD
Items with higher average scores	
2 - I feel my muscles are stiff	3.23±1.16
15 - Stress makes my symptoms worse	2.93±1.33
17 - I have little energy	2.89±1.04
18 - I have muscle tension in my neck and shoulders	2.80±1.24
12 - I sleep badly	2.63±1.37

Table 5. Dysfunctional beliefs related to pain

	% (n)	
	Yes	No
When the pain increases, do you believe that it is your body that is 'hurting more"?	96.60 (29)	3.40 (1)
Do you believe that exercise or movement makes your symptoms worse?	63.30 (19)	36.70 (11)
Do you believe that stress or anxiety can increase your pain?	80 (24)	20 (6)
Do you believe that imaging tests (e.g., radiography, magnetic resonance) can define and justify your condition?	93.30 (28)	6.60 (2)

At the end of the activity, the participants were asked about their satisfaction and about the importance of the theme for them, who responded on a Likert scale from zero to 10, with zero being negative/dissatisfied and 10 positive/satisfied. The average response for each item was as follows: 1 - How relevant do you think is the content of the class you attended? 9.80±0.48; 2 - What grade do you give for the way that this information was presented? 9.96±0.18; 3 - Do you consider it useful for other patients to know the content of this class? 9.80±0.80; 4 - Do you believe that understanding these facts will change the way you face your pain? 9.93±0.36.

DISCUSSION

Pain is an extremely prevalent symptom. A review of studies on the prevalence of CP in the Brazilian population found a range from 29.3 to 73.3%, affecting more women than men, and the most prevalent location was the dorsal/lumbar region[26].

The higher prevalence of CP in the elderly Brazilian population is significantly associated with being female, having less education, and worse economic status[27]. This socioeconomic influence also influences these people's resignation in reporting pain, and in their care[28]. In the studied population, the average age of patients with CP was 54.5±12.32 years old, most of them women, with an average family income of 1.64±0.73 minimum wages.

Among the behavioral aspects, 93.3% of the patients involved considered themselves to be sedentary, 44.4% live close to smokers, 50% consider the quality of their sleep bad, and 26.66% very bad. Higher prevalence of smoking was consistently observed in pain diagnoses, including fibromyalgia, back pain and headache, as well as physical inactivity and poor sleep quality, which contribute to a higher prevalence and worse outcome of chronic pain[13,14,27,29].

The largest number of complaints of CP was in the spine. In Brazil, the characteristics associated with the higher prevalence of spinal CP in both genders were increasing age, low education level, smoking history, high salt consumption, overweight and obesity, chronic diseases such as hypertension and high cholesterol[30]. Low back pain is heterogeneous in its presentation and its underlying mechanisms for the development and progression of symptoms. A vast literature describes biological, psychological, and social characteristics that explain individual variations in the presentation of the disease[31].

Among the biological aspects, variations in tissue disease, overload on tissues and structures by posture, muscle alignment, and activation, physical inactivity, pain neurology, central and peripheral changes in pain processing are implicated[32-34]. In the psychological domain, there is an equivalent diversity of associated factors such as the way the person deals with pain, self-efficacy, catastrophizing of pain, avoidance, kinesiophobia, depression, anxiety, anguish, and pain behavior, all having different implications within a treatment[35-37]. The social domain is equally diverse, including issues such as job satisfaction, support and social interaction[35,38].

CS can be defined as an amplification of neural signaling within the central nervous system that causes hypersensitivity to pain[39]. It corresponds to clinical diagnostic criteria where the pain complaint cannot be due to neuropathic pain due to injuries, neuropathy, diseases of the nervous system; or described as, for example, shooting, stinging, and not due to nociceptive or inflammatory processes such as pain proportional to the injury or identifiable inflammatory processes. Besides, it is necessary to have evidence of widespread pain and not just localized complaints, hypersensitivity to sensory processes in general, for example, sensitivity to light, sound, touch, odors etc., and symptoms that are a product and contributor to the construct "mental load" such as sleep problems, pain intensity, affective lability, cognitive difficulties and lack of energy and/or fatigue[40]. A set of symptoms commonly identified in patients with CP is the overlap of symptoms, including sleep disturbance, widespread pain, affective disturbance, cognitive disturbance and energy deficit[40,41].

The central sensitization inventory (CSI-BP) is a self-perception scale designed to alert health professionals that the symptoms presented by a patient may be related to some level of CS. The literature points out that the average scores on the CSI questionnaire in diseases with somatic characteristics are 40 points[42]. In this sample of 30 patients with CP, the average score on the CSI questionnaire was 49.86±16.14, with the questionnaire items with the highest score: 2 – "I feel my muscles are stiff"; 15 – "Stress makes my symptoms worse"; 17 – "I have little energy" 18 – "I have muscle tension in my neck and shoulders" and 12 – "I sleep badly." These findings show how much the overlap of multiple symptoms can be involved with the severity and impact of CP[43] among patients.

A study that analyzed the beliefs and attitudes related to chronic low back pain in the Brazilian population showed that the belief "physical injury" was the only one that presented a mean close to the desired orientation, that is, for these patients, pain is not necessarily related to a physical injury[43]. In this study, when asked whether they believe that when the pain is intense, their body is increasing, that is, connecting the pain to tissue injury, 96.60% of the volunteers reported that yes, so this direct relationship existed. When questioning the volunteers if they believe that stress or anxiety can increase and influence the painful experience, 80% responded yes, which was considered a desirable orientation. The three emotions most commonly associated with CP are depressed mood, anxiety and anger. These emotions, in turn, are associated with reduced pain thresholds, reduced pain tolerances and increased reported pain intensity[44-46]. However, this awareness

that emotions can influence the painful experience does not necessarily mean that they are aware of it, in order to try to modify or intervene in these emotional factors.

Fear of movement and other injuries may be a better predictor of physical functional limitations than the underlying biophysical or pathophysiological variables[47]. There is also strong evidence that the fear related to pain is more associated with the perceived disability and reduced behavioral performance than pain itself[48]. When asking the volunteers if they believe that exercise or movement makes their symptoms worse, 63.30% answered yes, characterizing fear related to movement.

When asked whether they believe that imaging tests such as radiography and magnetic resonance can define and justify their condition, 93.30% believe so, showing belief and dependence on imaging tests for diagnosis and prognosis by health professionals. Current studies point to the excessive use and reliance on imaging tests, which are often not accurate for establishing a diagnosis and correlating with the level of pain, including images in clinically healthy subjects[49-51].

The combination of education in pain with conventional forms of therapy is associated with improved function and pain in different populations[52-54]. So, the physical therapist's adequate knowledge is essential to act and guide the patient correctly.

The class on neurophysiological aspects of pain aimed to encourage reflection and reconceptualization of pain, recognizing dysfunctional behaviors and thoughts related to the painful phenomenon, in addition to clarifying myths in the care of CP for patients[55-58].

Both the content and the method of carrying out the activity were well accepted by patients who stated that the activity positively changed the way they see their health problem, in addition to considering it important that other patients with CP also receive the same guidance.

The limitations of this study were the difficulties of the service and the short time available for its execution, preventing further research on socioeconomic issues and the identification of other associated health comorbidities. Further studies on CP and its impact on vulnerable populations are needed, identifying the impact of low education, income and access to health services, and the extent to which these factors are determinant in the care of patients who complain of chronic pain.

CONCLUSION

The results reinforce the need for a biopsychosocial look at the management of chronic pain since the patient with CP does not present only biomechanical or musculoskeletal changes, but a broad spectrum of dysfunctions that cause and maintain pain. Pain education is a useful tool, with good acceptance by patients when they become aware of the multiple aspects that influence the painful phenomenon.

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Prevalence of orofacial pain in wind instrument players

Prevalência de dor orofacial em músicos de instrumento de sopro

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ABSTRACT

BACKGROUND AND OBJECTIVES: This cross-sectional observational study was conducted due to the uncertainties that still exist about the role of playing wind instruments in musculoskeletal complaints. Therefore, the objective was to assess the prevalence of temporomandibular dysfunction and associated factors in wind instrument players.
METHODS: Wind instrument players from the School of Music of Fine Arts of Paraná were evaluated for nine-months. Axes I and II of the Research Diagnostic Criteria for Temporomandibular Disorders was used to obtain the variables of interest. The statistical analyses were performed using the SPSS 2.0 software, using the Fishers Exact test, with a significance level of 5%.
RESULTS: Thirty-five musicians were examined, 85.7% were male, and 14.3% were female. The temporomandibular dysfunction prevalence was 51.4% being more commonly found in the group II (disc displacements) 34.2%. This result was statistically meaningful when associated with females (p=0,052). Group I disorders (muscle disorders) were diagnosed in 5 patients (14.2%) and group III disorders (joint disorders) were diagnosed in 3 patients (8.5%). Gender also influenced the presence of chronic pain, being more frequent in females (p=0.019).
CONCLUSION: In this research, we found a high prevalence of individuals affected by temporomandibular dysfunction. Therefore, studies with expanded samples are necessary, as well as educational and preventive measures. Temporomandibular dysfunction specialists should devote more attention to this group of people.
Keywords: Chronic pain, Facial pain, Occupational diseases, Syndrome of temporomandibular joint dysfunction.

RESUMO

JUSTIFICATIVA E OBJETIVOS: Estudo observacional transversal foi conduzido devido às incertezas que ainda existem sobre o papel de tocar instrumentos musicais de sopro nas queixas musculoesqueléticas. Portanto, o objetivo foi avaliar a prevalência de disfunção temporomandibular e fatores associados em músicos de instrumento de sopro.
MÉTODOS: Foram avaliados músicos de instrumento de sopro da Escola de Música Belas Artes do Paraná, durante o período de nove meses. Para obtenção das variáveis de interesse, os eixos I e II do instrumento *Research Diagnostic Criteria for Temporomandibular Disorders* foi utilizado. As análises estatísticas foram realizadas com o *software* SPSS 2.0, utilizando-se o teste Exato de Fisher, com nível de significância 5%.
RESULTADOS: Foram avaliados 35 músicos, 85,7% do sexo masculino e 14,3% do sexo feminino. A prevalência de disfunção temporomandibular foi de 51,4%, sendo mais comumente encontrado no grupo II (deslocamentos do disco) 34,2%. Esse resultado apresentou-se estatisticamente significante quando associado ao sexo feminino (p=0,052). Distúrbios do grupo I (distúrbios musculares) foram diagnosticados em 5 pacientes (14,2%) e distúrbios do grupo III (distúrbios articulares) foram diagnosticados em 3 pacientes (8,5%). O sexo também influenciou na presença de dor crônica, sendo mais frequente no sexo feminino (p=0,019).
CONCLUSÃO: Nesta pesquisa encontrou-se grande prevalência de indivíduos acometidos por disfunção temporomandibular. Portanto, é necessário o desenvolvimento de estudos com amostras ampliadas, bem como propagar medidas educativas e preventivas, sendo esse um público para o qual o especialista em dor e disfunção temporomandibular deve dedicar maiores cuidados.
Descritores: Doenças profissionais, Dor crônica, Dor facial, Síndrome da disfunção da articulação temporomandibular.

INTRODUCTION

Musculoskeletal pain is a frequent occupational risk in musicians[1]. Playing musical instruments that depend on the masticatory system can create an overload, causing increased tension in the masticatory muscles and temporomandibular joint (TMJ)[2,3]. This tension increase with continuous and frequent stimulation can trigger temporomandibular disorder (TMD)[4], characterized by pain, during masticatory muscle function, in the preauricular area and/or TMJ, limitation or deviation in the performance of mandibular movements; and presence of TMJ sounds (clicking or crepitus) during the function[5].

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There is growing interest in studying the relationship of TMD in musicians due to monotonous movements produced as a result of static and repetitive muscle work, and long training periods to which they are exposed. There is evidence that monotonous and repetitive movements combined with long training periods can affect the musculoskeletal structures of musicians, especially in the areas where the greatest muscular effort occurs[6] and may act as triggering and/or perpetuating factor for TMD[7]. Added to this is the performance-related anxiety and high-stress levels these professionals are often subjected to, which can exacerbate health problems among musicians, including musculoskeletal disorders[8,9].

It is unclear whether playing an instrument is directly or in combination with other factors associated with TMD[4]. This inaccuracy is exacerbated when restricted to the group of wind instrument musicians. Given the uncertainties that still exist about the association of playing this type of instrument in musculoskeletal complaints, this study aimed to investigate the prevalence of TMD in wind instrument musicians at the School of Music and Fine Arts of Paraná and to analyze the association between the presence of TMD with the time of practice and the type of instrument.

METHODS

An observational cross-sectional study following the principles of the Declaration of Helsinki and the norms for conducting observational studies STROBE[10-12]. Data collection was performed between March and November 2018. Thirty-five wind instrument musicians from the School of Music and Fine Arts of Paraná (UNESPAR), Curitiba, were included. All participants received research-related information that explained the study objectives as well as the benefits and risks to which participants would be exposed. Inclusion criteria were to be a wind instrument musician, to be enrolled at UNESPAR, and to be at least 16 years old. Exclusion criteria were individuals with chronic joint diseases.

The clinical examination was conducted according to the guidelines of the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD)[13], with the adoption of the validated Portuguese version. This study reported prevalence data of RDC/TMD axes I and II. TMD signs were assessed by clinical examination by a single examiner (E1) throughout the study, who received prior training by an experienced examiner (E2). The third researcher helped record the data during the examinations.

During the clinical examinations, the participants were kept in chairs in the institution's corridor (UNESPAR), under natural light, so that they were comfortable. Following the diagnostic criteria in the RDC/TMD research were evaluated: mouth opening amplitude, verified with the aid of a caliper; mouth opening pattern; joint noises; palpation of the masseter muscle in the bundles of origin, body, and insertion; temporal muscle palpation in the anterior, middle and posterior bundles and TMJ, lateral and dorsal pole palpation. Articular noises were detected by placing the index fingers on the TMJ during opening, closing, laterality, and protrusion movements. For muscle palpation, approximately 1kgf and 0.5kgf digital pressure was applied for joint palpation. Throughout the examination, the subject's head was firmly supported passively by the operator's hand. Before muscle and joint palpation, each participant was instructed to express the painful sensation as clearly as possible, if it existed. The instrument used classified pain at palpation in each of the muscle/joint areas as mild, moderate or severe, and assigned a score from 1 to 3 for the level of pain. An anamnestic record was prepared by the research team to obtain information about which wind instrument was used by the study participant, frequency and duration of the trials, the existence of breaks during training, exercises to relax the facial muscles after the practices.

Patients were diagnosed under one or more of the following conditions: muscle disorders (group I), disc displacement (group II), joint disorders (group III). Variables related to axis II of the RDC/TMD instrument that assess the presence of chronic pain, degree of disability, depression, and specific and nonspecific physical symptoms were also used. Patients diagnosed with a disorder and with pain complaints were referred to receive care at the Pain and TMD outpatient clinic of the Federal University of Paraná (UFPR).

The Research Ethics Committee of UFPR evaluated and approved this study under opinion CAAE 91294818.3.0000.0102.

Statistical analysis

Descriptive and inferential statistical analysis was performed using the SPSS 2.0 software using Fisher's exact association test. All inferential analyzes considered a significance level when $p \leq 0.05$.

RESULTS

Data were collected from 35 participants, 85.7% male, and 14.3% female (Figure 1). The average age of the participants was 27 years, ranging from 17 to 54 years old, distributed as follows: adolescents aged 16 to 19 years (25.7%), young adults aged 20 to 24 years old (22.9%), adults aged 25 to 59 years old (51.4%) and older people aged 60 and over (0%).

It was observed that 51.4% of the sample had at least one of the TMD diagnoses, distributed as follows: group I, muscle disorders, diagnosed in 5 patients (14.2%), group II disorders, disc displacements, diagnosed in 12 patients (34.2%), group III disorders, articular, diagnosed in 3 patients (8.5%) (Figure 2).

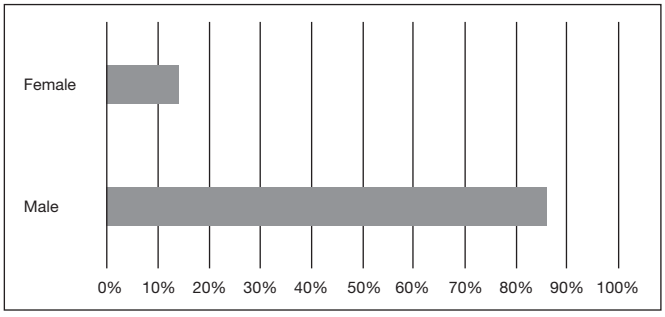

Figure 1. Distribution of the studied sample according to gender

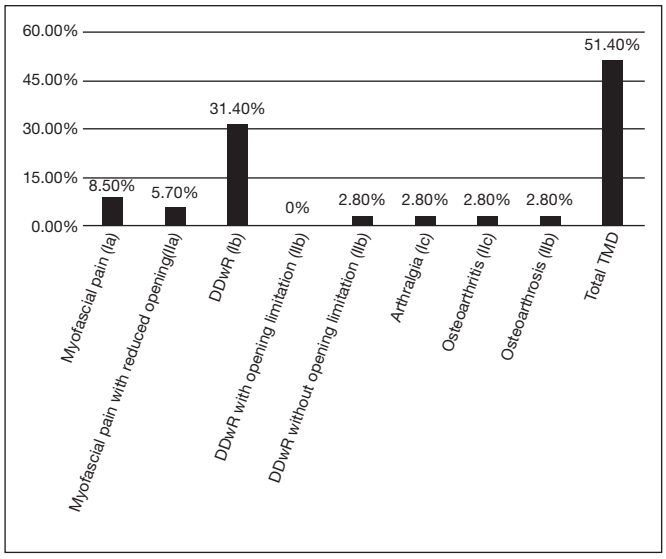

Figure 2. Sample distribution according to each diagnosis of temporomandibular dysfunction
TMD = temporomandibular disorder; DDwR = disc displacement with reduction; DDwoR = disc displacement without reduction.

Table 1. Prevalence of temporomandibular disorders in different groups according to gender

Diagnoses	Female		Male		p-value
	Yes	No	Yes	No	
Group I	1	4	4	26	0.561*
Group II	4	1	9	21	**0.052***
Group III	0	5	3	27	0.620*
Any TMD diagnosis	4	1	14	16	0.338*

Group I = muscle disorders; Group II = disc displacement; Group III = joint disorders. * Fisher's Exact test with significance level of 0.05. Bold value means statistical significance.

There was no significant difference in the prevalence of TMD between the different age groups, as age did not influence the occurrence of specific symptoms such as crackling, crepitus, teeth grinding, tired jaw sensation, tinnitus, a sensation of bite alteration, p=1), chronic pain (p=0.156) and depression (p=0.280).

Gender differences were found in the prevalence of diagnosis for group II, disc displacements, and this diagnosis was significantly more prevalent in females (p=0.052) (Table 1). Gender also influenced the presence of chronic pain, being more frequent in females (p=0.019); however, this study found no association between gender and the presence of depression.

The number of years the individual plays wind instruments did not influence the presence of TMD (Table 2). The number of hours of daily practice did not influence the presence of TMD, chronic pain, specific symptoms, and depression. Sixty-two percent of study participants reported regular practice of the wind instrument, while only 37.1% of them reported performing relaxation exercises during the practice; 51.4% mentioned warming up and 74.3% of them reported taking breaks between practices, however, none of these habits influenced the prevalence of TMD. The type of instrument also did not influence the presence of the disease (Table 3).

DISCUSSION

The prevalence of TMD in the general population is approximately 22%[14], with 51.4% of the sample affected with at least one of the TMD diagnoses. Other studies support the evidence that being a wind instrument musician is associated with a higher prevalence of TMD signs and symptoms. A previous study with these individuals, using the same diagnostic method, found a prevalence of 68.3% of participants with some type of TMD[15].

Table 2. Prevalence of temporomandibular dysfunction in different groups according to the musical practice time of the study participants

Diagnoses	≤ 3 years old		3 – 6 years old		6 – 9 years old		≥ 10 years old		p-value
	Yes	No	Yes	No	Yes	No	Yes	No	
Group I	0	7	1	4	1	4	3	13	0.746*
Group II	3	4	3	2	1	4	5	11	0.613*
Group III	1	6	1	4	0	5	1	15	0.626*
Any TMD Diagnosis	4	3	3	2	1	4	9	7	0.599*

Group I = muscle disorders; Group II = disc displacement; Group III = joint disorders. ≤ = less than or equal; ≥ = greater than or equal. * Fisher Exact test with significance level of 0.05.

Table 3. Prevalence of temporomandibular dysfunction in the different groups according to the musical instrument used by the study participants

Diagnoses	Cup-shaped mouthpiece		Simple edge instrument		Simple reed instrument		p-value
	Yes	No	Yes	No	Yes	No	
Group I	2	21	1	4	2	4	0.351*
Group II	6	17	4	1	2	4	0.061*
Group III	2	21	1	4	0	6	0.497*
Any TMD Diagnosis	9	14	4	1	4	2	0.185*

Group I = muscle disorders; Group II = disc displacement; Group III = joint disorders. Cup-shaped mouthpiece = trombone, stick trombone, bass trombone, tuba and trumpet; simple edge instrument = flute, transverse flute; simple reed instrument = clarinet and saxophone. * Fisher Exact test with significance level of 0.05.

A research that investigated the association between being a musician and having shoulder, neck and head pain, or having TMD symptoms, found results that support the association between the presence of TMD and the practice of woodwind instruments[16]. When comparing the prevalence obtained in this study with prevalence in other risk groups, such as high impact athletes, a study with professional of mixed martial arts showed that 61% of them had some type of TMD, while the prevalence among athletes of the Brazilian karate team was 54%[17]. One of the characteristics that these groups have in common is their frequent exposure to competition anxiety and stress. Future studies should investigate the real effect of this variable.

In this study, the most frequent diagnosis was found in group II, disc displacements (37.1%). The subgroup with the highest percentage of individuals affected was the disc displacement with reduction (DDwR) (28.5%). The diagnosis of DDwR without opening limitation was found in (2.8%) and no individuals with disc displacement without reduction (DDwoR) with opening limitations were identified. These results are similar to the findings of the research conducted with music students at the Professional School of Arts of Beira Interior, in which 68.3% of the individuals had some joint disease, 31.7% were diagnosed with disc anteposition with reduction and 14.6% diagnosed with disc anteposition without reduction, without opening limitation. In both studies, there were no musicians with no disc anteposition without reduction with opening limitation. As in both studies, the participants were in full musical activity; neither was in the acute phase of the injury, which would probably make the practice of music impossible and, consequently, would not be this individual in the environment in which the research was conducted[15].

When the relationship between the type of instrument used and the diagnoses was analyzed, there was a tendency for significance with group II diagnoses (p=0.061) and the use of metal instruments, namely: tuba (23.5%), trombone (14.7%), euphonium (5.8%), trumpet (17.6%) and French horn (5.8%), instruments in which sound is produced by direct vibration of the performer's lips over a mouthpiece. The need to apply forces to the stomatognathic system repetitively generates continuous mechanical stress, capable of producing microtrauma. The results found in this study are in line with previous research that quantified the strength in the perioral structures involved during the wind instrument's embouchure mechanism and concluded that metal players apply higher forces than wood-based musicians, the trombone being the one that requires greater application of force[18]. Also, in a study involving 150 wind instrumentalist musicians, in which imaging studies were performed using lateral cephalometric radiographs and cephalometric analysis, concluded that when the musician uses the tuba and trombone, the mandible moves from a resting position up and back repeatedly, favoring posterior displacement of the mandible condyle and increasing the likelihood of anterior dislocation of the articular disc[19].

Regarding the association found between gender and diagnosis for group II (p=0.052), it is known that the prevalence of TMD is higher in women, with a proportion of five women for each man being reported (5:1)[20]. One study suggests that women tend to have repositioned mandibular condyles when compared to men, which probably predisposes them to anterior disc displacements[21]. In this study, gender influenced the presence of chronic pain, being more frequent in females (p=0.019). However, this result should be interpreted with caution because the sample was primarily male, with only five women participating in the study, and two had pain. No association was found between gender and depression. It is unclear whether chronic pain predates depression or the other way around. The idea recently advocated would be a simultaneous coexistence of these two diseases, and depression is an element directly associated with the degree of disability generated by pain[22]. The results obtained in this study regarding gender should be interpreted with caution due to the small number of women included.

In this study, no significant associations were found in the prevalence of TMD among age groups, as well as the number of years of instrumental practice and the number of hours of daily training that did not influence the presence of TMD, chronic pain, specific symptoms and depression. However, a previous study found that the older the musician and the longer the practice, the higher the prevalence of joint TMD[15]. And this is due to the fact that effects of music practice are accumulated, which can trigger or aggravate a pre-existing TMD[15]. In addition, the number of hours, the presence of breaks, relaxation exercises and the instrument embouchure were analyzed. None of these factors influenced the presence of TMD, even though there are controversies in the literature, in which years of practice, age and number of hours are the main predisposing factors for the presence of dysfunction[23]. Possibly this association was not found due to the sample size and the individual characteristics of the participants.

The main limitations of this study were sample size and heterogeneity of gender distribution, so results should be interpreted with caution. However, it is important to note that a validated instrument was used for data acquisition and, in conjunction with the current literature, provides evidence that wind instrument musicians have a high prevalence of TMD.

CONCLUSION

Studies with a higher level of evidence should be developed in this population so that the real impact of using wind instruments on the development and maintenance of TMD can be elucidated, and specific prevention measures can be developed.

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Vibration associated with cryotherapy to relieve pain in children

Vibração associada à crioterapia no alívio da dor em crianças

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ABSTRACT

BACKGROUND AND OBJECTIVES: The administration of intramuscular drugs and peripheral venous puncture are procedures that use needles cause pain, especially in children. This painful experience generates distress, phobia, tachycardia, refusal to further treatments, anxiety, and sadness in parents. The use of non-pharmacological methods such as vibration and cold for pain relief in children has become a reliable alternative. The objective of this study was to evaluate the association between vibration and cryotherapy as a strategy for the relief of pain in children undergoing procedures with the use of needles.

CONTENTS: This is an integrative review, in which articles were searched in the Pubmed, Medline, BDENF and LILACS databases, using the descriptors: "Child", "Vibration", "Cryotherapy" and "Pain" associated with the Boolean operator "and". After the selection and reading of the articles in full, they were systematically synthesized and classified with a level of scientific evidence 2. Studies have shown that the association between vibration and cryotherapy is effective in reducing pain in children with or without cognitive alterations, also reducing their and parents' anxiety during procedures performed with needles.

CONCLUSION: The implementation of vibration associated with cryotherapy during the administration of injectable drugs and the installation of a peripheral venous device can reduce the fear, anguish, and anxiety in children, calming the parents and benefiting health professionals.

Keywords: Child, Cryotherapy and pain, Vibration.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A administração de fármacos por via muscular e a punção venosa periférica são procedimentos que utilizam agulhas e causam dor, especialmente em crianças. Essa experiência dolorosa gera angústia, fobia, taquicardia, recusa em tratamentos posteriores, além da ansiedade e desconforto na família. A utilização de métodos não farmacológicos, como a vibração e a crioterapia para o alívio da dor em crianças tem se tornado uma forte alternativa. O objetivo deste estudo foi avaliar a utilização da associação entre a vibração e a crioterapia como estratégia para o alívio da dor em crianças submetidas a procedimentos com a utilização de agulhas.

CONTEÚDO: Trata-se de uma revisão integrativa, na qual, buscou-se artigos nas bases de dados: Pubmed, Medline, BDENF e LILACS, com a utilização dos descritores: "Criança", "Vibração", "Crioterapia" e "Dor" associados entre si com o operador booleano "and". Após a seleção e leitura dos artigos na íntegra, os mesmos foram sistematicamente sintetizados e classificados com nível de evidência científica 2. Os estudos demonstraram que a associação entre a vibração e a crioterapia apresentou eficácia na redução da dor em crianças com ou sem alterações cognitivas, além de reduzir a ansiedade das crianças e dos pais durante os procedimentos executados com agulhas.

CONCLUSÃO: A implementação da vibração associada à crioterapia na administração de fármacos injetáveis ou na instalação de dispositivo venoso periférico, pode reduzir o medo, a angústia e a ansiedade nas crianças, tranquilizando os pais e beneficiando os profissionais de saúde.

Descritores: Criança, Crioterapia e dor, Vibração.

INTRODUCTION

Pain is defined as an unpleasant human experience related to the activation of the somatosensory nervous system after the occurrence of a real or potential injury[1]. Invasive procedures that use needles, such as peripheral venipuncture and injection of drugs, including immunobiologicals, cause undesired psychological, physiological, and emotional effects on children, causing stress on family and health professionals[2].

Child compliance and family agreement with the treatment are potentially compromised due to the need for procedures that cause discomfort and pain[3]. The implementation of non-pharmacological measures to relieve the pain caused by needle procedures facilitates the continuity of treatment by the child due to the reduction of stress and distress in these patients[4].

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The use of vibration associated with low temperature (cryotherapy) as a non-pharmacological strategy to relieve the pain caused by needle procedures has been widely studied and is well accepted by the health team, the child and the family, as it decreases the occurrence of painful events, being easy to apply and considered a low-cost measure[2,5].

The physiological mechanisms of pain relief provided by vibrating movements and cryotherapy are related to the sharing of synapses in the spinal cord. The nerve fibers conduction the pain stimulus shares the synaptic pathways with the thermal conduction fibers activated by thermoreceptors (temperature-sensitive) and with the mechanic conduction fibers, activated by mechanoreceptors (stimulated by the vibration). The interference of this interneuronal response inhibits the pain stimulus, causing relief[6,7].

Studies have shown that the use of cryotherapy is effective in relieving the pain generated by the intravenous administration of botulinum toxin in patients with facial dystonia and women during labor[8,9]. Vibratory stimulation has been shown to be beneficial in relieving muscle pain caused by intense physical exercise and during intravenous administration of local anesthetics in patients[10,11]. Evidence points to the benefit of pain relief in children when combining vibration and cryotherapy in procedures using needles[2,5].

The motivation of the present study arose from the perception of a gap in critical reflections in the literature about the importance and effectiveness of cryotherapy associated with vibration as a non-pharmacological intervention to relieve pain, anxiety, and stress in children, caused by therapies that require the use of needles.

Therefore, this study aimed to evaluate the use of the association between vibration and cryotherapy as a strategy for pain relief in children undergoing procedures using needles.

CONTENTS

A bibliographic and descriptive study, characterized as an integrative review to identify and analyze, in scientific production, the use of vibration associated with cryotherapy to relieve pain in children. This study followed six methodological steps: 1. Determination of the theme and selection of the research hypothesis or question for the construction of the integrative review; 2. Elaboration of criteria for the selection of studies/samples; 3 Definition of the information to be extracted from the selected studies and categorization of the studies; 4 Evaluation of included studies; 5 Interpretation of the results and 6. Presentation of the review[12].

This review was structured to answer the following guiding question: What is the effect of the association of vibration with cryotherapy to relieve pain in children undergoing needle procedures?

The literature search was performed in the Pubmed, Medline, BDENF (Nursing Database) and LILACS databases from November 2018 to March 2019, using the following controlled keywords: "Child", "Vibration", "Cryotherapy" and "Pain", as well as their English correspondents, interconnected by the Boolean operator "AND".

The inclusion criteria were published studies, with access to the full textual content that addressed the researched theme, papers with sample comprising children and adolescents (zero to 18 years old), and written in Portuguese, English, or Spanish. The exclusion criteria were review articles, experience reports, theses, dissertations, animal model studies and samples composed of adults. There were no restrictions based on year of publication.

After searching the databases, a total of 94 articles were found, which initially went through the selection and analysis steps in order to delineate the sample of the present review.

The publications were selected in four interrelated stages. During the first round, articles that were not available with full-textual content (n=4) were excluded, and later, papers with duplicate databases (n=11) were eliminated. In the second-to-last stage, studies that did not address the study objective after reading the title and abstract (n=66) were excluded. Subsequently, the articles were carefully and critically read in their entirety using structured records in an adapted instrument, and, at this stage, five (n=5) papers were excluded due to the use of dental procedures in adults[5]. The study selection flowchart is shown in figure 1.

After selection, eight articles were included and coded in descending order of year of publication (N1 - N8) and systematically synthesized as to authors, year of publication, purpose, methods, strategies, and main results (Tables 1 and 2).

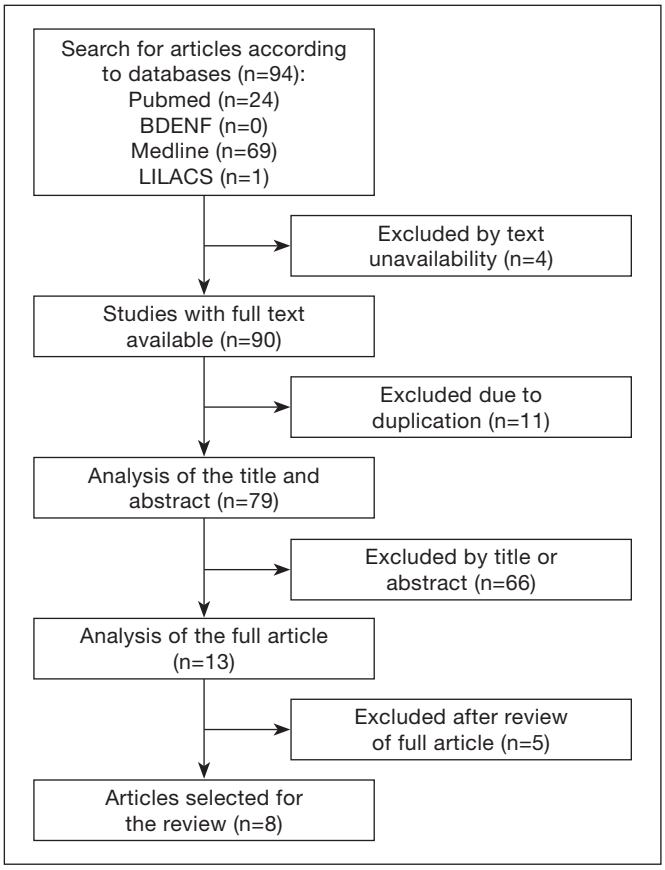

Figure 1. Selection of the studies

Table 1. Summary of studies included in the review

Code	Authors	Origin	Objectives	Methods
N1	Bergomi et al.[2]	Italy	Evaluation of vibration associated with cryotherapy with or without the use of cartoons to relieve pain in children undergoing venipuncture. Evaluation of parents' anxiety regarding these pain relief interventions.	150 binomials (5-12-year-old children and their parents) were randomly divided into four groups: 1. control group, which did not undergo any pain relief intervention, 2. Buzzy® group, 3. Buzzy® group associated with drawing and 4. cartoon group. All children underwent peripheral venipuncture.
N2	Redfern, Chen and Sibrel[20]	United States States	To determine if vibration associated with cryotherapy was able to relieve pain in children undergoing immunization.	Fifty children and adolescents (5-18 years old) were randomly divided into two groups: 1. group using Buzzy® and 2. group without the device, both submitted to immunization by intramuscular route.
N3	Moadad et al.[3]	United States States	To investigate the use of vibration and cryotherapy in pain relief during peripheral venous catheter insertion in children.	48 dyads (children aged 4 to 12 years and their mothers) were randomly divided into two groups: 1. control group (not exposed to Buzzy®) and 2. group using Buzzy®. Both groups were comprised children whose treatment required passing a peripheral venous catheter.
N4	Schreiber et al.[21]	Italy	To test the effectiveness of using cryotherapy associated with vibration to relieve the pain induced by peripheral venipuncture in children with cognitive impairment.	71 children with cognitive impairment were randomly allocated to two experimental groups: 1. control, in which they were not exposed to Buzzy® and group 2 children submitted to Buzzy®. Both groups underwent peripheral venous device installation.
N5	Canbulat Sahiner et al.[14]	Turkey	To determine the effect of cryotherapy associated with vibration in relieving the pain and anxiety triggered by immunization against diphtheria, tetanus, and infections caused by pertussis in children.	104 school-age children (up to 7 years old) were randomly divided into two groups by a computer program: 1. control group that was not exposed to Buzzy® and 2. group that was subjected to Buzzy®. The pain stimulus was established by the administration of the vaccine (DTP) to the deltoid muscle, 5cm above the site of the Buzzy® device.
N6	Canbulat, Ayhan and Inal[22]	Turkey	Evaluation of the effect of cryotherapy associated with vibration on pain and anxiety in children undergoing peripheral venous catheter installation.	176 children aged 7 to 12 years were randomly divided into two groups using a computer program: a control group, which was not exposed to Buzzy®, and the group with Buzzy®, 5cm above the peripheral venipuncture site.
N7	Inal and Kelleci[23]	Turkey	To investigate the effect of cryotherapy associated with vibration to relieve the pain and reduce the anxiety in children during blood collection for laboratory tests.	120 children from 6 to 12 years of age were randomly divided into two groups: 1 control group that was not stimulated with Buzzy® and group 2, with children submitted to Buzzy®, both groups underwent the installation of a venous catheter to collect blood.
N8	Baxter et al.[18]	United States States	To test the effectiveness of cryotherapy associated with vibration in relieving pain and anxiety in children and adolescents undergoing peripheral venipuncture for blood collection.	81 children and adolescents aged 4 to 18 years were randomly divided into two experimental groups: 1. control group, which was not stimulated with Buzzy® and 2. group exposed to Buzzy®. Both underwent the installation of a peripheral venous catheter to collect blood.

Table 2. Summary of strategies and main results of the studies

Code	Strategies	Main results
N1	The vibration associated with cryotherapy was induced by the Buzzy® device, whether or not associated with the cartoon. The perception of pain in children was assessed by the Wong-Baker faces scale, which was also used by nurses who performed the procedure. The nurses also assessed the pain in children using the emotional manifestation scale. Parents' anxiety was assessed using the numerical scale from zero to 10.	The vibration associated with cold and cartoons minimized the pain in children submitted to venipuncture. These pain control interventions also contributed to reducing parents' anxiety.
N2	Vibrating stimulation and cryotherapy were established by Buzzy®. The pain was measured in the groups using the Wong-Baker faces scale, and a modification of this scale allowed the assessment of children's anxiety. Parents' satisfaction was investigated based on the experience with the study by applying a questionnaire and assigning a score that ranged from poor to excellent.	Anxiety showed no difference between the groups. The pain was much lower in the vibration and cold group compared to the control group. There was no statistical difference in the assessment of parents' satisfaction between the groups.

Continue...

Table 2. Summary of strategies and main results of the studies – continuation

Code	Strategies	Main results
N3	The pain stimulus was established by peripheral venipuncture. And thermal (cryotherapy) and vibration stimulation were promoted by the Buzzy® device. Pain assessment in children occurred by applying the Wong-Baker faces scale by researchers, parents, and the nurse who installed the peripheral device. These answers were compared.	Vibration associated with cryotherapy was effective in reducing pain in children undergoing peripheral venous device insertion. The researchers, nurses, and parents' assessment was similar in attesting pain relief in these children.
N4	The pain was induced by the installation of a peripheral venous catheter, and the Buzzy® device was used to cause the vibration associated with cryotherapy. Pain assessment was measured using the pain verification scale in non-communicative children, surgery version.	Children who received vibration associated with cryotherapy showed a reduction in pain in the peripheral venous catheter installation.
N5	The pain was promoted by intramuscular vaccine administration and the vibration stimulation associated with cryotherapy was provided by the Buzzy® device in both groups. Each child was assessed for pain by two examiners: one nurse who applied the vaccine and one researcher using the Wong-Baker faces scale and verbal pain report. Anxiety was assessed using the child's fear scale.	The association of the vibration stimulation and cryotherapy was effective in reducing pain and anxiety in children undergoing immunization against diphtheria, tetanus, and infections caused by pertussis.
N6	The Buzzy® device was used for vibration stimulation associated with cold. Pain stimulation and anxiety were stimulated by the insertion of a peripheral venous catheter. Pain assessment was conducted using the Wong-Baker faces scale and the visual analog scale. The child's anxiety was assessed by their parents based on behavioral and verbal analysis.	The application of cryotherapy associated with vibration is effective in reducing the pain and anxiety in children, generated by the venipuncture necessary to pass a peripheral venous catheter.
N7	The vibration stimulus associated with cryotherapy was given with the Buzzy® device, 5cm above the puncture site throughout the procedure. Anxiety and pain were assessed by the anxiety and pain scales, as well as by the revised faces scale applied by the researchers.	The group using the Buzzy® device showed reduced anxiety and pain compared with the control group.
N8	Buzzy® was the device used for vibration stimulation associated with cryotherapy, placed 5cm above the puncture site. Anxiety and pain were assessed by the anxiety and pain scales for children, both applied by the researchers.	Low temperature associated with vibration reduced the pain in children and adolescents undergoing peripheral venipuncture compared to the control group that received no stimulation.

All studies were in English, developed in the following countries: United States (n=3), Turkey (n=3), Italy (n=2), and classified as level 2 of scientific evidence[13]. All studies used the cryotherapy associated with the vibration device, Buzzy®, which has the shape of a bee, whose body emits vibratory waves, and the wings are cooled to reduce the local temperature. The device was placed 5cm from the site of the needle insertion[2,5].

DISCUSSION

Needle procedures are the main causes of pain in children, especially in the age group from 5 to 10 years of age, and trigger behavioral, psychological, physiological and emotional changes that have a major impact on health, such as phobia, anxiety, tachycardia, sadness, and hormonal changes. Such events may compromise the drug therapy in these patients, especially the child's resistance to future treatments, as well as the anxiety of the family and health professionals[3,14].

The implementation of pain relief measures in children undergoing needle procedures is important and increasingly necessary, as it promotes the child and family compliance with subsequent treatments, reduces fear, and reframes the meaning of care. Pain relief can be achieved with the use of pharmacological measures that favor the reduction of pain perception with the use of drugs or with non-pharmacological measures, which are widely studied in children[15,16].

Many non-pharmacological pain relief strategies are effective during the clinical management of hospitalized children, among them the use of therapeutic toys, the use of cartoon, non-nutritive sucking, and especially the association of vibration with cryotherapy[15,17].

The effectiveness of vibration and cryotherapy in reducing pain is related to the blockage of the afferent receptive nerve fibers to pain stimuli (A-delta and C fibers) and also to the stimulation of the non-nociceptive A-beta fibers, which activate the inhibitory interneurons reducing the conduction of the pain information to the spinal cord in the central nervous system[18,19].

All studies (N1-N8) showed that the association of vibration with cryotherapy reduced the pain related to the use of needles during treatment in children. In addition, studies (N5, N6, and N7) also reported a reduction in the child's anxiety during the procedure, which did not occur in study N2, which also evaluated anxiety during the procedure in these patients[2,3,14,18, 20-23].

Most studies (N1, N3, N5, N6, N7, and N8) used the Wong-Baker faces scale to assess the pain in children in different groups. Only one study modified this scale (N2)[20], which

adapted it to analyze the anxiety level in addition to pain in children. Study N4[21] was the only study developed with children with cognitive impairment. Pain assessment in these children was performed using the pain verification scale in non-communicative children, in the surgery version[2,3,14,18,22,23]. Other pain assessment scales were used in association with the Wong-Baker faces scale. In study N1[2], nurses assessed pain in children through the emotional manifestation scale; study N6 used the visual analog scale, and studies N7[23] and N8[18] used the anxiety and pain scale. Study N5[14] assessed the pain stimulus by the child's verbal report.

Two studies investigated parent-related aspects of the participating children. N1[2] assessed parents' anxiety using a numerical scale ranging from zero to 10 and found that the parents' anxiety was lower in the group of children with the Buzzy® device. Study N2[20] assessed parents' satisfaction using a structured questionnaire, but there was no difference between the groups of children with or without the device.

Family engagement is important and should be encouraged and implemented during the application of pain relief techniques in children, since family bonding is one of the main factors contributing to the child's comfort and stress reduction, facilitating the professional's job[16].

CONCLUSION

The use of non-pharmacological measures for pain relief in children is a strategy well accepted by health professionals and parents when the child undergoes procedures that cause distress and pain. It was evident that vibration associated with cryotherapy reduced the pain and anxiety in children, with or without cognitive impairment, undergoing interventions that require the use of needles, and this fact explains the reduction of parents' anxiety and the satisfaction of the health professionals. -

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Gender role in pain perception and expression: an integrative review

Papel do gênero na percepção e expressão da dor: revisão integrativa

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ABSTRACT

BACKGROUND AND OBJECTIVES: Gender seems to play a role in influencing the response to experimental pain, although this influence is not very clear yet. Therefore, the objective of the present review was to investigate the contribution of the gender construct (gender identity/role) in the experience of pain through the selection and analysis of clinical studies on the subject.

CONTENTS: A search was carried out in the databases Medline (via Pubmed), LILACS (via BVS), and PsycINFO. The search used the following descriptors: gender identity, pain, gender role combined by the Boolean operator AND/OR (gender identity) AND pain AND gender role AND pain, in English, Portuguese and Spanish. At the end of the selection, 11 studies were included for this review. All the investigations recovered on the subject are clinical laboratory studies. Regarding the influence of the gender identity and its role in pain perception, most of the studies (91%) show that this variable was a contributing factor to the differences observed in perception (tolerance/pain threshold) and the need to communicate the pain.

CONCLUSION: In experimental pain, a higher degree of femininity or female social roles are associated with lower thresholds and less tolerance to pain, as well as a greater natural tendency to communicate pain sensation. These results are independent of the type of stimulus, ethnicity, or sexual orientation.

Keywords: Gender and health, Gender identity, Pain.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A identidade de gênero e o seu papel aparentam influenciar a resposta à dor experimental, embora ainda não seja claro a magnitude dessa influência. Assim, o objetivo deste estudo foi investigar a influência do construto gênero (identidade/papel de gênero) na experiência da dor mediante a seleção e análise de estudos clínicos sobre o tema.

CONTEÚDO: Foi desenvolvida uma busca nas bases de dados Medline (via Pubmed), LILACS (via BVS), PsycINFO. A busca foi desenvolvida com os seguintes descritores: *tender identity, pain, gender role* combinados pelo operador booleano *AND/OR* (gender identity) *AND pain OR* (gender role) *AND pain*. Os idiomas selecionados foram inglês, português e espanhol. Ao final da seleção, 11 estudos foram incluídos. Todas as investigações recuperadas sobre a temática compreenderam estudos clínicos laboratoriais. Em relação à influência da identidade e papel de gênero na percepção dolorosa, a maioria dos estudos (91%) encontraram que essa variável foi fator contribuinte para as diferenças observadas na percepção (tolerância/limiar de dor) e necessidade de comunicar a dor.

CONCLUSÃO: Em dor experimental, maior feminilidade ou papéis sociais femininos estão associados a menores limiares e menor tolerância à dor, assim como maior propensão de comunicar a sensação dolorosa. Esses resultados independem do tipo de estímulo, da etnia ou orientação sexual.

Descritores: Dor, Gênero e saúde, Identidade de gênero.

INTRODUCTION

Pain is a symptom present in a wide range of medical conditions and can have a significant impact on a person's quality of life and overall functioning[1]. Women have a higher prevalence of chronic pain-related diagnoses[1-4], and research has consistently shown gender differences, such as pain perception, description and expression, the use of coping strategies, and the benefit of different treatments[2,5-7]. Biological differences may contribute to gender differences[2,3,7]. Genetic factors, as well as hormonal factors, act as gender-specific pain mediators[2,3,5]. Studies indicate that women's pain responses are affected by the menstrual cycle, pregnancy, and oral contraceptive use[5,8-10], which considers that hormones are related to pain response. Additionally, the response to opioid receptor antagonists may generate differences in pain experiences between men and women[3,5,10].

Pain is, by definition, always subjective[11]. Scales, widely used to assess pain in research and clinical practice[2,12,13], measure pain reporting, which in turn may be influenced by psychosocial factors such as gender. From an early age, boys and girls are socia-

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lized along with gender norms of how to respond to pain. Boys and men learn to be tough, tolerate pain, and sustain painful experiences, while girls and women are socialized to be sensitive, caring, and to verbalize discomfort[14].

The terms "sex" and "gender" refer to two distinct but related factors. Sex encompasses a set of biological attributes such as chromosomes, gene expression, and anatomical aspects. Gender refers to the attitudes, feelings, and behaviors that a given culture associates with a person's biological sex. It is related to a complex context, being dependent on psychological, psychosocial, cultural, and political factors, being defined as a sociocultural construction of roles, norms, behaviors, identities, and power relations[15,16]. Gender identity refers to a person's inner sense of being man, woman, female or male, or otherwise. Gender expression refers to how a person reports gender identity to others through behavior, clothing, hairstyles, voice, or body characteristics. In turn, the role of gender refers to the way society, in a given time or culture, considers the femininity/masculinity of the individual[17].

Despite the growing literature on the theme, few studies have been conducted to identify the influence of gender on pain. Understanding the mechanisms associated with these differences may, in the future, provide more realistic data for epidemiological studies and direct to more specific treatments.

This study aimed to investigate the contribution of the gender construct (gender identity/role) in the pain experience by selecting and analyzing clinical trials on the theme.

CONTENTS

In order to achieve the proposed objectives, an integrative literature review was chosen, a method that provides the synthesis of knowledge, as it enables the gathering of results from significant studies. The steps that guided its development were: 1- elaboration of the guiding question, 2- establishment of inclusion and exclusion criteria of articles, 3- definition of the information to be extracted from the selected studies, 4- critical analysis of the included studies, 5- analysis, synthesis and presentation of results[18].

The guiding question of the research was: "what is the contribution of gender in pain responses and experiences for both sexes"? Study selection was limited to publications in English, Portuguese, and Spanish. Reviews and meta-analyses were excluded from the sample. The last consultation of the publications was between June and August 2018. The selected databases were Medline (via Pubmed), LILACS (via VHL), and PsycINFO. The search was performed with the following keywords: 'gender identity', 'gender role' and 'pain' combined by boolean operator OR/AND (((gender identity[MeSH Terms]) *OR* gender roles[MeSH Terms])) AND pain[MeSH Terms]. Original studies involving humans, without age limit that used in their methodology some instrument to assess gender identity or gender role, and/or femininity and/or masculinity, and the relationship with pain were included.

The selection of publications was conducted in three phases: double-reading title selection, abstracts, qualitative analysis of the full texts. The analysis process for the assessment and selection of articles was performed by two researchers independently, with subsequent comparison of results to obtain the texts selected by consensus. A third researcher evaluator was invited to participate in cases of disagreement or doubts about the inclusion of the work.

At the end of the selection process, 123 articles listed in Medline and four in LILACS were identified, four of which were duplicates. After the double-reading of title selection, 42 articles were selected, and 81 articles were excluded. After reading the titles and abstracts of these articles, 27 references were selected for the full reading. Eleven studies were included in the qualitative synthesis. The process of study selection can be observed in figure 1.

The titles were excluded for: not contemplating the theme (81); studies evaluating only gender (15); studies that did not evaluate the relationship between gender and pain (16) and duplicates (4).

At the end of the selection, 11 studies were included. All investigations retrieved on the theme comprised of laboratory studies. Regarding the years of publication, the distribution was one article for the years 2002, 2003, 2004, 2006, 2012, 2013, 2014, and two for the years 2009 and 2011. In the analysis of the countries that investigated the theme, the distribution was as follows: United States (7), Israel (2), and the United Kingdom (2).

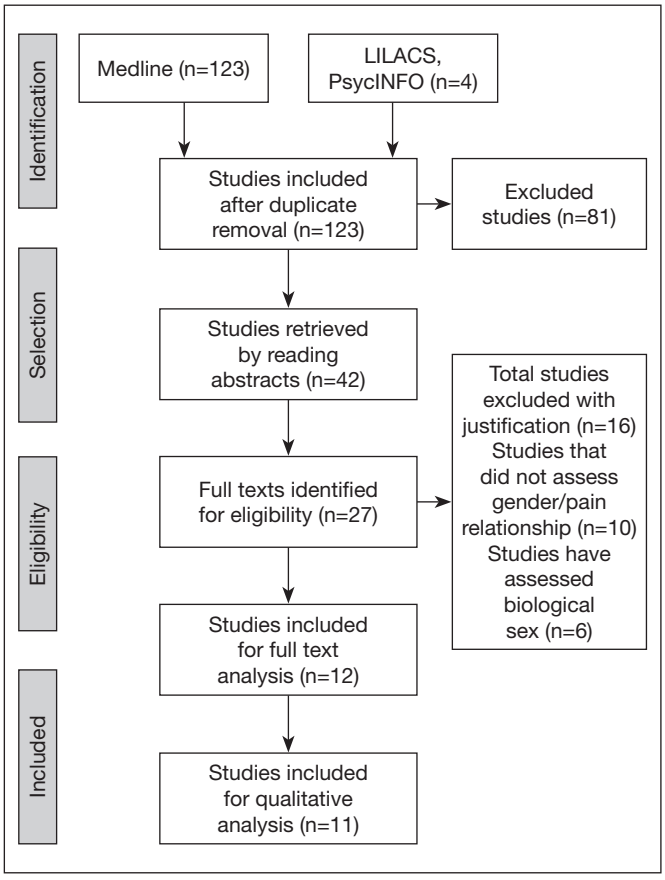

Figure 1. Identification of studies according to databases and eligibility criteria[19]

The study sample ranged from 67 to 548 participants. Concerning the age group, ten studies were with adult individuals (18-45 years old) and only one with children (8-18 years old). Regarding the study design, all articles were of the clinical trial type, with nine prospective nonrandomized, one prospective randomized, and one retrospective nonrandomized.

Seven different instruments were identified to assess gender identity and role. Most (six) used the Gender Role Expectation of Pain (GREP). The Bem Sex-Role Inventory (BSRI) was used in two studies, while the other studies used distinct instruments: Personal Attributes Questionnaire, Hypermasculinity Index, Child Sex-Role Inventory, and Balanced Inventory of Desirable Responding. One study applied questions about gender expression, the level of masculinity/femininity preferred for a romantic partner, how one describes oneself concerning masculinity/femininity.

For pain analysis, the most used instrument was the visual analog scale (VAS) in seven articles. Other research has applied different instruments: Short-Form of the McGill Pain Questionnaire, Pain Tolerance Assessment, and Quantitative Somatosensory Testing. Only one study did not use a standardized instrument. The pain threshold was sensitively measured by pain tolerance time.

All studies were with healthy subjects, where the pain was caused by different types of stimuli. The most frequently used stimulus was thermal (six studies). Also, other studies caused the pain sensation by pressure, ischemia and/or electric shock. Regarding the influence of gender identity and its role on pain perception, most studies (91%) found that this variable was a contributing factor to perceived differences (pain tolerance/threshold) and the need to report pain. The results are presented in table 1.

Table 1. Distribution of studies

Authors	Study design	n (M/W)	Gender assessment	Pain assessment	Applied stimulus	Results
Vigil, Rowell and Lutz[20]	Prospective, nonrandomized clinical trial	172 (W) Heterosexual, lesbian and bisexual	Masculinity/ Femininity self-identification	VAS	Ischemic	Among heterosexual women, attraction to more feminine romantic partners was associated with lower pain scores. In the group of lesbians and bisexuals with greater masculinity, higher pain and tolerance thresholds were observed.
Alabas, Tashani and Johnson[21]	Prospective, nonrandomized clinical trial	175 124 Libyans (62/62) 51 British (25/26)	GREP	VAS	Pressure/ ischemic	Males had lower scores for pain sensitivity and lower propensity to report pain, as well as higher pain tolerance.
Alabas, Tashani and Johnson[22]	Prospective, nonrandomized clinical trial	114 (56/58)	GREP	VAS	Thermal (cold)	Despite cultural differences, they did not influence responses to pain. Libyan (African) women were more likely to report pain, more sensitive and less tolerant. Libyan men showed greater tolerance and thresholds for cold pain.
Defrin, Eli and Pud[23]	Retrospective, nonrandomized clinical trial	548 (210/338) 341 Jews 105 Arab Muslims 102 Arab-Christians	GREP	VAS	-	Regardless of the religious ethnic group, the "typical" man considered woman to be more sensitive to pain. Men considered themselves less likely to report pain.
Fowler et al.[24]	Prospective, randomized clinical trial	89 (45/44)	BSRI/PAQ	Short-Form of the McGill Pain Questionnaire	Thermal (cold)	Sex and gender roles interacted in such a way that men reported lower pain sensitivity and less anxiety, but only when prepared with a female gender role.
Defrin, Shramm and Eli[25]	Prospective, nonrandomized clinical trial	72 (33/39)	GREP	HPT/ HPTL	Thermal (heat)	Individuals with greater masculinity had greater pain tolerance and less need to report pain.
Reidy et al.[26]	Prospective, nonrandomized clinical trial	195 (65/130)	Hypermasculinity Index	Pain Tolerance Assessment	Electric	Pain tolerance was significantly and positively related to traits of aggression in men, unlike women.
Myers et al.[27]	Prospective, nonrandomized clinical trial	240 (120/120)	Child Sex Role Inventory	VAS	Pressure/ thermal (cold/heat)	For boys, but not among girls, there was a significant negative correlation between masculinity and pain scores; as the masculinity score increased, pain self-reports decreased.

Continue...

Table 1. Distribution of studies – continuation

Authors	Study design	n (M/W)	Gender assessment	Pain assessment	Applied stimulus	Results
Robinson et al.[28]	Prospective, nonrandomized clinical trial	67 (37/30)	GREP	VAS	Thermal (heat)	The propensity to report pain was a significant predictor of the magnitude of temporal summation, regardless of sex. Women showed greater temporal summation to thermal stimuli.
Wise et al.[29]	Prospective, nonrandomized clinical trial	148 (61/87)	GREP	VAS	Thermal (heat)	Expectations related to male gender were predictors of higher pain thresholds and pain tolerance, regardless of gender.
Myers et al.[30]	Prospective, nonrandomized clinical trial	104 (54/50)	BSRI	Tolerance time in seconds	Thermal (cold)	Although the gender role was a predictor of pain tolerance, it was not a predictor of pain differences between the sexes.

VAS = visual analog scale; GREP = Gender Role Expectation of Pain; BSRI = Bem Sex Role Inventory; PAQ = Personal Attributes Questionnaire; HPT = Heat-Pain Threshold; HPTL = Heat-Pain Tolerance Limit.

DISCUSSION

This review aimed to identify whether gender (gender identity or roles) influences pain perception. According to the criteria used for the inclusion of studies, only investigations of experimental pain in healthy individuals could be retrieved. Most studies indicated that gender was a contributing factor to the differences observed in pain perception, despite the different stimuli applied. In general, the results showed an association between a higher degree of femininity and a greater perception of painful stimuli, regardless of gender. For individuals with a higher degree of masculinity, higher thresholds and pain tolerance were observed, as well as a lower propensity to report pain.

In all studies analyzed, the variables considered in experimental pain included: pain induction method, pain measurements used, laboratory environment influences, typified experimenter appearance, and possible individual biases. Due to the multiple sources of variability, it was evident that inconsistent patterns of pain responsiveness exist in the literature. Differences in the reporting of experimental pain in men and women are believed to result from an influence of the laboratory environment, where psychosocial constructs are activated differently between the sexes. Differences may be due mainly to gender-specific socialization patterns concerning pain beliefs, expectations, and subsequent behaviors. Thus, men who adhere to the male role are expected to underreport pain. On the other hand, following a female role would allow women to verbalize their pain reports. However, these reports are mainly speculative and the lack of controls in the studies makes it difficult to conclude on sex differences.

Although biological mechanisms have been postulated to explain these variabilities, it is suggested that social learning may be a stronger influence on pain response. During puberty, incipient gender differences in pain tolerance seem especially attributable to lower pain threshold in girls. Decreasing thresholds for girls may reflect specific changes in pain perception and pain assessment associated with puberty (due to hormonal influences or changes in gender role orientations). Another point that should be emphasized is that the individual's pain threshold did not influence pain resistance. A person reporting early pain experiences during a stimulus is also expected to experience decreased resistance. However, there seems to be a low correlation between pain threshold and resistance[32]. Social norms dictate that men should be stoic, making it unlikely that they report pain or express it emotionally. On the other hand, social rules allow women to be emotionally expressive when in pain and seek medical attention to relieve it.

Thus, one should be able to predict pain-related behaviors of an individual's gender group and the relative importance of adhering to group norms.

For gender analysis, most studies applied the GREP instrument designed to identify sexual differences in relation to pain expectations, both for others and themselves. This instrument analyzes five factors: pain sensitivity, willingness to report pain, pain sensitivity self-report, pain resistance self-report, and stereotyped pain resistance. The results of this study indicated that in all interventions, GREP mediated different pain reactions for both men and women. Based on social learning theory, men must tolerate more severe pain. Women also consider men, in general, to be more tolerant to pain, less willing to report pain, and less sensitive to it[32].

To a lesser extent, for the gender assessment, the BSRI instrument was applied in two studies. One study pointed out that while gender was a predictor of pain tolerance, it was not a predictor of pain differences between the sexes. In fact, the authors stated that the construct identified by BSRI is a global measure related to personality traits. Considering that gender-related pain behavior is flexible and context-dependent; therefore, the BSRI would not assess gender aspects that are specifically elucidated in the experimental pain task[33]. In another study that used the same painful (cold) stimulus and the BSRI instrument for gender assessment, it was observed that men reported lower pain sensitivity and less anxiety compared to women, but only when "prepared" with a female role. For example, the ability to bear pain may be amplified by the presence of a female suggestion. Men would show a higher tolerance for an experimental pain stimulus after being informed in advance that women have a higher tolerance in that situation[34].

As observed in the results (Table 1), a smaller portion of studies analyzed other possible confounding variables, such as ethnic and cultural differences, and sexual orientation. However, they

did not influence the response to pain. In a systematic review of racial and ethnic differences in experimental pain sensitivity, the authors noted that experimental and racial/ethnic differences in experimental pain sensitivity are more pronounced in supra-threshold pain experiences than in thresholds. This may be important because supraliminal pain measures have been reported as one of the most relevant experimental tasks for clinical pain[34]. This study elucidated some aspects pertinent to experimental pain, which behavior differs significantly from clinical pain, especially chronic pain. It is noteworthy that pain threshold and pain intensity classifications are commonly considered indicative of the sensory-discriminative pain characteristic, while tolerance and discomfort classifications are considered indicative of the affective and motivational aspects of pain. The results of this study highlight the importance of further studies on clinical pain that assess the gender construct in its self-identification and behavioral aspects to understand the higher prevalence and higher risk of chronic pain in females. Factors such as the examiner's qualities should also be better reported in studies. Although it is difficult to control all confounding variables, it is essential to identify the biological and social aspects related to the participants' gender to understand the phenomenon better.

CONCLUSION

In experimental pain, higher femininity or female social roles seem to be associated with lower pain tolerance and lower pain tolerance thresholds, as well as a greater propensity to report painful sensation. These results do not depend on the type of stimulus, ethnicity or sexual orientation.

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The use of opioids in the treatment of oncologic pain in the elderly

O uso de opioides no tratamento da dor oncológica em idosos

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ABSTRACT

BACKGROUND AND OBJECTIVES: The use of opioids in cancer is already widespread and proven by several well-controlled clinical trials. However, the elderly with cancer pain are=undertreated due to the lack of knowledge in the management of these patients, the underestimation of pain, as well as the fear of complications arising in this age group. Therefore, the scientific community contributes to giving inputs to create possible clinical and health guidelines. The present study aimed to perform a systematic literature review of opioid treatments proposed for cancer-related pain in elderly patients.

CONTENTS: The search on the literature included papers addressing cancer pain treatment with opioids among the elderly, published from 2008 to 2018, and available in Portuguese or English. Searches were conducted on Medical Literature, Analysis, and Retrieval System Online (MEDLINE) and Latin American and Caribbean Health Sciences Literature (LILACS) electronic databases using the keywords "cancer pain", "opioids", and "elderly" in both languages, combined with the Boolean operator "AND". To analyze the quality of the method, the adapted Critical Appraisal Skills Programme was used. Of a total of 411 studies found, 32 were included. About 75% of the selected articles were published in the last five years.

CONCLUSION: The results showed that opioids remain the pillar to treat cancer-related pain in the elderly. They can be used for better management of pain, but with caution due to the possible adverse effects. In addition, pain management in the elderly requires a multifactorial analysis, including comorbidities, polypharmacy, and patient functionality. Therefore, an individualized approach in the elderly patient is required in order to enhance results, reduce side effects, and improve quality of life.

Keywords: Cancer pain, Elderly, Opioids.

RESUMO

JUSTIFICATIVA E OBJETIVOS: O uso de opioides em dor oncológica já é amplamente difundido e comprovado por diversos ensaios clínicos bem controlados. Entretanto, os idosos com dor oncológica são subtratados pela falta de conhecimento no manejo, a não valorização álgica nesses pacientes, bem como o receio das complicações advindas nesse grupo etário. Portanto, contribui a comunidade científica, dando substrato para a elaboração de possíveis diretrizes clínicas e de saúde. Este estudo teve como objetivo realizar uma revisão sistemática da literatura sobre o tratamento farmacológico com opioides proposto para dor oncológica em pacientes idosos.

CONTEÚDO: A busca na literatura incluiu artigos sobre o uso de opioides para o tratamento da dor oncológica em idosos, publicados entre 2008 e 2018, disponíveis em português ou inglês. Foram conduzidas buscas nas bases eletrônicas de dados Medical Literature, Analysis, and Retrieval System Online (MEDLINE) and Latin American and Caribbean Health Sciences Literature (LILACS) utilizando os descritores "dor oncológica", "opioides" e "idoso" em ambas as línguas, combinados com o operador booleano "AND". Para a análise da qualidade metodológica, foi utilizado o Critical Appraisal Skills Programme adaptado. Do total de 411 estudos resultantes, foram incluídos 32. Cerca de 75% dos artigos selecionados foram publicados nos últimos cinco anos.

CONCLUSÃO: Os resultados demonstraram que os opioides continuam sendo o pilar no tratamento da dor oncológica em idosos. Podem ser usados para o melhor gerenciamento da dor, mas com cautela por causa dos possíveis efeitos adversos. Além disso, o manejo da dor em idosos requer uma análise multifatorial incluindo as comorbidades, a polifarmácia e a funcionalidade do paciente. Portanto, é necessário tratar de modo individualizado o paciente idoso com o intuito de maximizar os resultados, diminuir os efeitos adversos e melhorar a qualidade de vida.

Descritores: Dor oncológica, Idosos, Opioides.

INTRODUCTION

Aging is a worldwide phenomenon. Over the next 43 years, the number of people over 60 will be three times higher than the current one[1]. The elderly population in Brazil has also been growing exponentially. By 2030 there will be 41.5 million older people or 18% of the population[2]. Due to this, population aging has been one of the major public health challenges, because as people get older, they are more likely to develop or contract chronic diseases such as cancer, as risk factors accumulate for certain types of this disease[3]. Currently, more than 70% of cancer cases worldwide occur in

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the elderly[4]. Therefore, there is an increase in the prevalence of chronic health problems and disabilities associated with the population of this age group, involving important specificities such as multimorbidities, polypharmacy, and their complications[3].

In elderly cancer patients, pain is the most prevalent symptom, as about 80% of them report some kind of painful sensation. Inadequate pain treatment can have serious consequences, both individually and socially[5-8].

Pain management should be performed according to the three-step analgesic ladder proposed by the World Health Organization (WHO) in the 1980s[9], in which opioids are recommended for the treatment of moderate to severe pain[8,10].

In addition to limited evidence for opioid use in elderly patients, there are still barriers such as fears, myths, and stigmas regarding this type of prescription[5,10-12].

Therefore, this study aimed to conduct a systematic literature review addressing the use of opioids in the treatment of cancer pain in the elderly. The study also aimed to explore the repercussions of opioid use in pain treatment, as well as its main barriers to adequate management in this population.

CONTENTS

This study was conducted as a systematic literature review following the guidelines established by Preferred Reporting Items for Systematic Reviews and Meta-analyzes (PRISMA).

In order to achieve a systematic literature review, the research question was initially established considering the proposed theme, i.e., the use of opioids in cancer pain treatment in the elderly, thus classifying individuals over 60 years. Then, between March and December 2018, searches were done in the Medical Literature, Analysis, and Retrieval System Online (MEDLINE) and Latin American and Caribbean Health Sciences Literature (LILACS) electronic databases, aiming at gathering and evaluating the main articles on the use of opioids for cancer pain treatment in the elderly, published between 2008 and 2018, available in Portuguese or English, using the descriptors "cancer pain," "opioids", and "elderly" and their respective Portuguese terms, all present in the Health Science Descriptors (DeCS) and Medical Subject Headings (MeSH), combined with the Boolean operator "AND".

The criteria used for articles inclusion were: a) articles concerning the proposed theme, i.e., the use of opioids in cancer pain treatment in the elderly; b) articles published between 2008 and 2018; c) articles in Portuguese or English; d) articles available in full; e) articles on randomized studies, systematic reviews and observational studies; f) articles that met the criteria proposed by the Critical Appraisal Skills Program (CASP) checklist for qualitative research.

Exclusion criteria were a) articles addressing a non-pharmacological treatment of pain; b) articles describing animal studies; c) dissertations, theses and case reports; d) repeated articles among electronic databases.

The articles were categorized, allowing the gathering of information such as identification of the original article and its authors, journal, year of publication, database, methodological characteristics, level of evidence, measured interventions, and results found. The critical analysis of the data obtained in the studies was performed after the organization of the selected articles. The CASP instrument was applied to ensure the methodological rigor, relevance and credibility necessary for an integrative review of studies with different approaches.

Searches in the MEDLINE and LILACS electronic databases resulted in 411 articles published between 2008 and 2018. The initial evaluation was performed by reading the title, excluding 321 articles that did not present the theme "opioids in cancer pain treatment in the elderly". Then, the remaining 90 articles with inclusion potential were previously selected for evaluation of their abstracts according to the eligibility criteria. Three independent reviewers read the abstracts, and the publications that met the inclusion criteria were then fully assessed. In total, 32 articles were selected for this study; 75% were published in the last five years (Figure 1, Table 1).

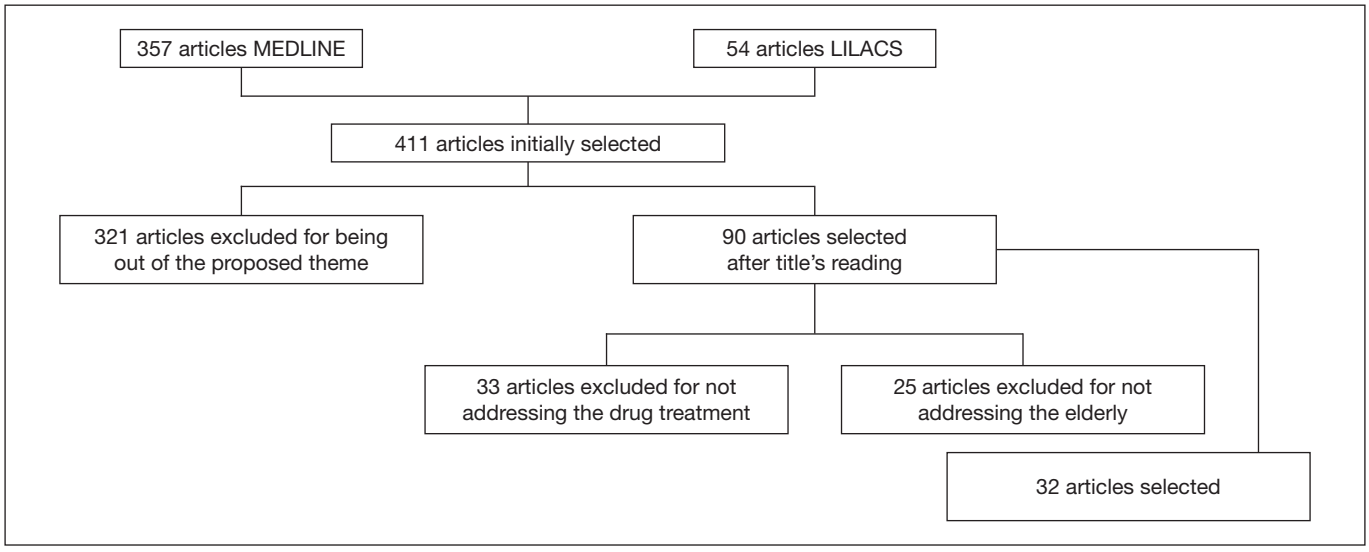

Figure 1. Data collection

Table 1. Selected articles

Authors	Purpose	Methodology	Therapy	Conclusion
Passik[13]	Assess long-term opioid therapy, including unmet needs, risks, and solutions	Literature review	Opioids	Chronic pain and abuse of prescribed opioids are common and substantially affect patients, doctors, and the society. Aggressive treatment of chronic pain should be balanced with the need to minimize the risks of opioid abuse, misuse, and deviation.
Wilson et al.[11]	Examine the prevalence of pain, its perceived severity, and its correlation across a range of physical, social, psychological, and existential symptoms.	Multicenter study addressing cancer patients' pain and assessing 21 other symptoms and concerns		Continued pain is a problem for many cancer patients under palliative care, especially in younger individuals approaching death
Paice and Ferrell[8]	Review available pain management treatments considering the individual needs of patients as well as special populations, including the elderly, cancer survivors, patients with addictive diseases, and those at the end of life.			The urgent need to address cancer pain issues emerged in oncology in the 1970s, largely influenced by the introduction of palliative care (PC). PC providers demonstrated that pain could be relieved, and failure to do so meant the decreased quality of life. Over the past 30 years, cancer pain relief has become a priority in oncology. Despite significant advances, there are still continuing barriers to quality of care and pain relief. There are many resources to assist doctors in treating cancer pain.
Rangel and Telles[5]	Address the principles for cancer pain treatment, as well as barriers related to patients, health professionals, and the health system.	Literature review		All physicians should be familiar with the use of analgesics. Opioids should not be prescribed just because the patient has a fatal disease, but according to the intensity of his/her pain.
Hennemann-Krause[14]	Present the rational use of analgesic drugs, highlighting their indications, doses, adverse effects, and proper care for the adequate prescription of common analgesics and opioids for the control of chronic cancer pain.	Literature review	Common analgesic drugs and opioids	Opioids prescription should not be done because the patient has a fatal disease, but according to the intensity of the pain.
Madadi et al.[15]	Identify patterns and characteristics among opioid users	Qualitative study	Opioids	New susceptible groups of opioid users with related cause of death were identified. The first evidence to help quantify the contribution of opioid misuse to user mortality in Canada
Srisawang et al.[16]	Assess the knowledge and attitudes of physicians and policymakers/regulators regarding the use of opioids for cancer pain management.	Cross-sectional study	Opioids	Continued education for physicians and conference organization is required for policymakers/regulators. Special education and training should be addressed to clarify the terms of physical addiction.
Zeppetella[17]	Known non-parenteral opioid formulations, such as sublingual fentanyl, which can provide faster and more effective relief from transitory exacerbation cancer pain.	Systematic review	Non-parenteral opioids, such as sublingual fentanyl	Fentanyl formulation available at doses of 100, 200, 400, 600 and 800 µg approved for the treatment of transitory exacerbation pain in opioid therapy tolerant adult cancer patients for underlying persistent cancer pain
Kraychete, Siqueira and Garcia[18]	Discuss recommendations for opioid use in newborns, children and the elderly	Systematic review	Opioids	The use of opioids at extreme ages is still a challenge. However, continued education around the subject is needed, stimulating clinical research and the creation of evidence-based recommendations. The safe use of these agents in the correct indication and proportion for pain relief decreases risks and should be the basis of sound clinical conduct.

Continue...

Table 1. Selected articles – continuation

Authors	Purpose	Methodology	Therapy	Conclusion
Nunes, Garcia and Sakata[19]	Assess the use of morphine as the first drug for moderate cancer pain treatment in patients with advanced disease and/or metastasis, as an option to the recommendations of the WHO-recommended analgesic ladder.	Randomized controlled study	Morphine	The use of morphine as the first drug for pain treatment did not promote a better analgesic effect than the WHO-recommended ladder, and there was a higher incidence of adverse effects.
Rocha et al.[20]	Analyze the self-care of older people living with cancer in outpatient treatment, from the perspective of their autonomy	Qualitative and descriptive research		The autonomy for self-care of the elderly is manifested in the concern with food, knowledge of the body's limits, changes imposed by living with cancer, and family support.
Kim et al.[21]	Assess pain response to opioid rotation or opioid combination in patients with uncontrolled cancer pain	Randomized study	Opioids	For patients with chronic uncontrolled cancer pain, both opioid rotation and combination strategies appear to provide significant pain relief and better patient satisfaction.
Reticena, Beuter and Sales[22]	Understand the experiences of the elderly with cancer pain	Qualitative research based on Heidegger's phenomenology, with recorded interviews		Cancer pain has biopsychosocial repercussions for the elderly, generating changes in their life activities and requiring holistic and authentic care.
Reyes-Gibby, Anderson and Todd[6]	Determine the risk of opioid misuse among emergency services for cancer pain patients and assess the demographic and clinical factors associated with increased risk of opioid abuse.	A cross-sectional study with a convenience sample	Opioids	The risk of opioid misuse among cancer patients is substantial. Tracking misuse in emergency departments is feasible
Coluzzi et al.[10]	Review some basic principles of opioid analgesia based on experience and knowledge of current publications on this care	Literature review	Opioids	Establish titration, individualization, and gradual reduction, along with the application of other good medical practice and clinical experience/judgment, including non-pharmacological approaches, can assist health care professionals in the effort to achieve optimal pain treatment.
Galicia-Castillo[12]	Manage chronic pain safely in the elderly	Literature review		A complete assessment, including description and management of pain, comorbidities, physical examination, and diagnostic tests are required for patient control. It is also important to inquire about the history of substance abuse.
Cella et al.[23]	Assess the prevalence of pain and opiophobia in cancer patients.	A cross-sectional study with patients undergoing exclusive cancer clinical treatment in an outpatient cancer hospital	Opioids	A high prevalence of moderate to severe pain was found in the observed patients, as well as a high prevalence of opiophobia.
Lin et al.[24]	Examine Taiwan's opioid prescribing standards for cancer patients to discover their potential concerns	Review of claims in the Taiwan National Health Insurance database for cancer-diagnosed patients from 2003 to 2011	Opioids	The use of strong short-acting opioids increased during the study period. Instead of oral opioids, transdermal fentanyl was the most commonly used opioid among cancer patients in Taiwan.
Oosten et al.[25]	Study the pharmacokinetics of subcutaneous and transdermal fentanyl and assess relays between subcutaneous and transdermal uses	Cohort study	Subcutaneous and transdermal fentanyl	Absorption may lead to fluctuations in plasma transdermal and subcutaneous fentanyl concentrations. Relay schemes are not applicable for subcutaneous and transdermal fentanyl rotations
Reddy et al.[26]	Determine the relationship between the equivalent daily dose of morphine and the dose of transdermal fentanyl in opioid rotation	Retrospective study	Morphine and transdermal fentanyl	The median rotation rate of transdermal fentanyl for the equivalent daily morphine dose was 100 mg/day and 2.4 µg/h, suggesting that 100 µg/h is equivalent to the 240 mg daily morphine dose.

Continue...

Table 1. Selected articles – continuation

Authors	Purpose	Methodology	Therapy	Conclusion
Barbera et al.[27]	Verify whether opioid prescriptions changed among older adults after 2007, in the context of changing opioid regulations, and whether effects were different among patients with a history of cancer	Elderly patients stratified annually into three groups: no history of cancer, diagnosed with cancer for more than 5 years and diagnosed with cancer for 5 years or less. Trends over time have been assessed per year for 1) opioid prescription rate, comparing trends before and after 2007; 2) average daily dose of opioid	Opioids	Decreasing prescription rates have been observed in some drug subclasses. The potential impact of these changes on the quality of symptom control for cancer patients requires further investigation.
Bennett, Paice and Wallace[28]	Understand the comprehensive management of cancer pain, including a thorough assessment, along with the use of pharmacological, non-pharmacological, integrative, and interventional therapies.	Literature review	Pharmacological, non-pharmacological, integrative, and interventional therapies	Although cancer pain remains prevalent, it remains undertreated, partly due to the concerns about opioid use. Opioids' efficacy in advanced disease is already clearly established; however, there are still issues about opioids' safety and efficacy in long-term cancer survivors.
Haider et al.[29]	Assess changes in the opioid type and prescription dose among patients who are referred by oncologists to an outpatient palliative care clinic	Review of electronic patient health records at new CP Outpatient Consultations between January 1 and April 30 of each year from 2010 to 2015. Demographic data, cancer type, and stage, symptom assessment, performance status, opioid data were collected. Opioid type and dose defined as the equivalent daily dose of morphine	Opioids	Over the past few years, the equivalent daily dose of morphine prescribed by reference oncologists has decreased. Following hydrocodone reclassification, the use of tramadol with less stringent prescription limit increased
Kuip et al.[30]	Summarize the multiple factors studied that potentially influence fentanyl pharmacokinetics focusing on implications for cancer patients	Systematic review	Fentanyl	Although aging may influence the fentanyl pharmacokinetics, sound conclusions are difficult to draw. There is at least a risk of lower clearance and, therefore, greater accumulation in elderly patients. Therefore, fentanyl should be titrated with caution in elderly patients.
Lee et al.[31]	Assess the non-inferiority of oxycodone/naloxone compared to controlled-release oxycodone for cancer pain control	Randomized, open, phase IV, parallel-group clinical trial	Oxycodone/naloxone and oxycodone	The group receiving oxycodone/naloxone was no lower than the one receiving oxycodone in terms of pain reduction after 4 weeks of treatment and had a similar safety profile.
Nosek et al.[32]	Compare analgesia and adverse effects during oral administration of morphine and oxycodone, transdermal fentanyl and buprenorphine in cancer and pain patients	Randomized clinical trial	Morphine, oxycodone, transdermal fentanyl, and buprenorphine	All opioids were effective and well-tolerated. Morphine was the most effective for pain improvement compared to some of the questionnaire items regarding the negative impact of pain on patients' daily activities.
Schmidt-Hansen et al.[33]	Assess the efficacy and tolerability of oxycodone in any pain administration route in adults with cancer.	Systematic literature review	Oxycodone	For clinical purposes, oxycodone or morphine may be used as first-line oral opioids for pain relief in cancer adults.
Yen et al.[7]	Assess the efficacy and safety of proportional doses of fentanyl oral soluble film in patients with transitory exacerbation cancer pain.	An open, non-comparative multicenter study	Fentanyl oral soluble film	The dose of fentanyl oral soluble film proportional to the opioid regimen for basal pain treatment is effective and well-tolerated for the treatment of patients with transitory exacerbation cancer pain.

Continue...

Table 1. Selected articles – continuation

Authors	Purpose	Methodology	Therapy	Conclusion
Guitart et al.[34]	Assess the effect of sublingual fentanyl tablets for pain relief, quality of life and adverse effects in cancer pain patients according to cancer stage and basal opioid regimen	Qualitative study	Sublingual fentanyl tablets	Subgroup exploratory analyses demonstrate the efficacy and safety of sublingual fentanyl tablets for treating transitory exacerbation cancer pain, regardless of cancer stage and basal opioid regimen.
Masel et al.[35]	Document the feasibility of fentanyl oral tablets for the treatment of patients with transitory exacerbation cancer pain.	Prospective study	Fentanyl oral tablets	Treatment with fentanyl oral tablets led to quick pain relief and reductions in the number of episodes of transitory exacerbation cancer pain. Patient satisfaction was rated as excellent or good.
Peng et al.[36]	Compare the efficacy and adverse effects of patient-controlled intravenous analgesia with hydromorphone, sufentanil, and oxycodone in the treatment of patients with advanced cancer and pain.	Retrospective serial study	Patient-controlled intravenous hydromorphone, sufentanil, and oxycodone	There was no significant difference in analgesic effect and adverse effect between hydromorphone, sufentanil, and oxycodone.
Yamada et al.[37]	Assess the effect of continuous pain management interventions and opioid-induced adverse effects on outpatients with cancer	Systematic review	Opioids	Pharmacist interventions can help to adequately achieve the management of pain and adverse effects through interviews and ongoing assessments of cancer patients prior to consultations with physicians, which underlines the importance of pharmacist interventions.

DISCUSSION

The aging process is one of the factors that leads to the increased incidence of cancer, as there are inherent physiological changes that jointly cause molecular changes. These changes are combined with mitogenic factors that, associated with the insufficiency and dysregulation of the immune system that is characteristic of this age group, favor cell proliferation and, consequently, the onset of cancer[38].

The physiological changes caused by aging also significantly affect the metabolism of administered drugs, especially opioids. Thus, healthcare professionals should be aware of the following factors: patient susceptibility to adverse drug effects, iatrogenic cascade, adverse drug reactions, hospitalization, and institutionalization, as well as polypharmacy commonly found in the practical reality of the elderly.

Usually, as a result of aging, organs and systems have less functional reserve. Therefore, they present particularities involving the pharmacokinetics and pharmacodynamics of drugs regarding absorption, distribution, metabolism and excretion variables (Table 2).

Pain is an unpleasant experience associated with tissue or potential injury, with sensory, emotional, cognitive, and social components. In turn, persistent pain is more complicated in

Table 2. Pharmacological changes due to aging

Absorption	Distribution
Reduction of: • Splanchnic blood flow • Gastric secretion • Absorption surface • Gastrointestinal motility Increased gastrointestinal pH	Reduction of: • Plasma volume (8%) • Cardiac output • Body water (25%) • Plasma albumin (20%) • Replacement of muscle mass with fat (30 to 40%) Increased gastrointestinal pH
Metabolism	**Excretion**
Reduction of: • Liver mass • Hepatic blood flow (40%) Change in enzymatic activity (cytochrome P450) Change in phase I of metabolism (hydroxylation, oxidation, hydrolysis, and n-demethylation)	Reduction of: • Kidney mass • Number of functional nephrons • Renal blood flow (1-2% per year, reaching 50% in old age) • Glomerular filtration (30 to 50%) Increased incidence of spontaneous glomerular sclerosis

Source: Adapted from the Brazilian Society of Geriatrics and Gerontology[38].

the elderly than in younger patients. Up to 40% of elderly outpatients report pain, and this symptom affects 70-80% of patients with advanced cancer[5].

For cancer pain treatment, it is necessary to know its classification. Didactically, pain can be divided into two main types: 1) nociceptive, which represents tissue damage; 2) neuropathic due to nervous system's injury or dysfunction as a result of abnormal activation of the nociceptive route. Also included in this analysis are the local effects of tumor growth and local invasion, as well as the effects of auxiliary therapies such as chemotherapy and radiotherapy, as well as other complications. Therefore, in cancer patients, mixed pain prevails[5,38].

Pain complaints can be both precursors for cancer diagnosis as a consequence of the treatment adopted. Most of the time, pain is identified by the patient him/herself and not by health care professionals.

It is noteworthy that not only cancer involvement, but also the aging process lead to limitations in the body's physiological functions. Thus, the elderly are more predisposed to dependence on other individuals for self-care, loss of autonomy, and deterioration of quality of life. In this environment, as the evaluation of painful conditions in the elderly is a multidimensional experience, it encompasses several domains, including sensory, cognitive, affective, behavioral and sociocultural ones. Given this, the importance of pain management using validated protocols and scales is evidenced in order to provide the most appropriate treatment according to the patients' individual particularities[5,39].

However, there is not yet a single and exclusive standard instrument for the elderly that allows for global pain assessment and is free of bias and measurement errors, as there are different variables involved, such as patient interpretations of pain, expectations regarding the problem and its treatment. Notably, good anamnesis, detailed physical examination, and analysis of external factors are fundamental for the adoption of appropriate conduct.

From a general perspective, the WHO[9] analgesic ladder is the most widely used. In specialized services, one-dimensional scales such as face and verbal numeric scales are employed, as well as multidimensional scales such as Geriatric Pain Measure (GPM), McGill Pain Questionnaire (MPQ), Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC), and Pain Assessment in Advanced Dementia (PAINAID)[38].

Cancer pain can be controlled with simple treatments in more than 80% of cases. In the other 20%, however, it is necessary to adopt a multidisciplinary approach, with a careful reassessment of pain and the use of auxiliary drugs and/or non-pharmacological interventions for its control[5,38]. Regarding pharmacological treatment, opioids are among the most powerful and widely available drugs, constituting the pillar for the treatment of moderate to severe cancer pain[7,12,19].

Recent clinical guidelines and recommendations on the management of patients with advanced cancer emphasize the importance of adequate pain relief with the use of opioid analgesics to improve their quality of life. It is essential that patients are continuously informed about the goals of pharmacological therapy and regularly reevaluated during treatment[7].

The American Geriatrics Society has come to consider the use of opioids as an effective and sometimes indispensable option for treating pain in elderly patients. This is due, among other factors, to the potentially serious adverse events associated with the use of anti-inflammatory drugs, such as diclofenac and ibuprofen and COX-2 inhibitors (COXIB), such as celecoxib[12].

Opioids mimic the action of endogenous opioid peptides. They may suppress the activation of presynaptic and postsynaptic tension-dependent calcium channels or activate post-synapse potassium channels. This suppression results in decreased excitability and suppression of neuron activity-dependent transmitter release or adenylyl cyclase action, reducing the impulses to the brain and spinal cord[12,14].

The four major opioid receptor subtypes are mu-opioid receptor (MOP), delta-opioid receptor (DOP), kappa opioid receptor (KOP), and nociceptin peptide factor (NOP). Clinically used opioids are mostly MOP selective, although they may also interact with other receptors if administered at high doses[14]. Indeed, elderly cancer patients suffering from severe pain may benefit from the use of strong opioids such as fentanyl, morphine, oxycodone, hydromorphone, methadone, buprenorphine, among others (Table 3).

Table 3. Opioid analgesics

Drugs	Presentation, doses	Therapeutic doses/interval	Effects (start/peak/end)
Fentanyl	Patches 5, 10 and 20 mg	5–20 mg/7 days	24 hours/72 hours
Morphine	Capsules, 10 and 30 mg Oral solution, 10 mg/mL Ampoules, 1 mL-10 mg/mL	5–200 mg/4 hours (oral dose)	15 min/2 hours/4 hours
Morphine LC	Capsules, 30, 60 and 100 mg	30–100 mg/8 to 12 hours	1 hour/6 hours/14 hours
Oxycodone	Capsules, 10, 20 and 40 mg	10–40 mg/12 hours	1 hour/8 hours/25 hours
Hydromorphone	Extended release tablet, 8, 16 and 32 mg	8-32 mg/24 hours	6 to 8 hours/24 hours
Methadone	Capsules, 5 and 10 mg Ampoules, 10 mg/mL	10-50 mg/6 to 12 hours	1 hour/12 hours/25 hours
Buprenorphine	Patches, 5, 10 and 20 µg	5–20 µg/7 days	18 to 24 hours/72 hours/7 days

Source: Adapted from the Brazilian Society of Geriatrics and Gerontology[38].

Fentanyl

Transdermal fentanyl is a potent, long half-life agonist opioid with lipophilicity. It is very suitable for patients unable to use the oral route due to odynophagia and/or dysphagia, with persistent nausea and vomiting, in situations that may lead to bronchoaspiration, intolerance to morphine and other opioids, and due to its ease of use. Its use is recommended in patients with constant pain but little episodic pain. After the patch placement, effective analgesia start lasts 12 to 24 hours. The action time of each patch is 72 hours, remaining for 12 to 18 hours after its removal. The transmucosal formulation has short action duration, non-invasive administration route, and tolerable safety profile[14,17,25,26,34,35].

Morphine

Morphine is indicated for pain classified as moderate to severe, with good results in pain of nociceptive or somatic origin, as 85% of them respond to this drug. It has a potent analgesic effect, short half-life, with therapeutic analgesia interval of 4 to 6 hours, without ceiling and linear effect, i.e., the higher the dose, the greater the analgesia. It is well-absorbed by the gastrointestinal tract, with action onset within 20 to 40 min. It undergoes hepatic metabolism and renal elimination, and only a small part is eliminated by the gallbladder. It does not generally accumulate in tissues and the free fraction in plasma is dialyzable. However, in patients with impaired renal function, it has a stronger effect and longer action duration, because there is an accumulation of active metabolites, especially morphine-6-glucuronide[6,14,19,29,32,39].

Oxycodone

Oxycodone is a MOP agonist in the brain and spinal cord and has some activity in KOP. It goes through the first-pass metabolism[26]. It is the preferred drug for change when morphine fails to provide effective pain relief but may also be recommended as a first-line drug for severe cancer pain control[14,31].

Hydromorphone

Hydromorphone hydrochloride is intended for single-dose administration. It is a potent MOP agonist, showing a poor affinity for KOP. It is the only opioid that has controlled single-phase release and promotes continuous dose-dependent analgesia during the 24 hours interval between two doses. It is moderately water-soluble, has hepatic metabolism and urinary excretion. Its primary metabolite is hydromorphone-3-glucuronide (H3G), in which concentrations are approximately 27-times higher than those of the original drug, indicating that H3G has a smaller volume of distribution and/or lower clearance[7,14].

Methadone

The methadone is a synthetic opioid, agonist of MOP, KOP, DOP, and N-methyl D-Aspartate (NMDA) receptor. It appears to block serotonin and norepinephrine reuptake. It is a lipophilic drug, which analgesic effect usually lasts from 6 to 8 hours and may reach up to 24 hours. Its analgesic power can be up to five to 10 times higher than morphine. Its oral absorption is quick and almost complete, and its metabolism occurs mainly in the liver. Methadone and its metabolites can be eliminated by feces and urine. Renal excretion of methadone decreases with time of use and can, therefore, be used in patients with chronic kidney disease. It causes less nausea, constipation and sedation than morphine. However, the interaction between methadone and other drugs is more frequent than with morphine[14,40].

Buprenorphine

The buprenorphine is a thebaine derivative, 25 to 40 times more potent than morphine. Its action mechanism is suggested to occur by partial agonist effects on MOP and KOP, as well as antagonistic action on DOP. It is found in intravenous, sublingual and transdermal presentations, the latter being the only one available in Brazil. The patches come in the 5, 10 and 20 µg/h presentations, which are released within seven days. It has no systemic accumulation and its elimination occurs mainly through the intestinal tract and is therefore considered safe in patients with renal failure[6].

FINAL CONSIDERATIONS

Considering the main strong opioids described, it is noteworthy that pain intensity is not adequately assessed in approximately 50% of cancer patients. Besides, adverse effects of opioids, such as nausea, vomiting and constipation, may be limiting factors for the use of these drugs, leading to their early discontinuation and consequent inadequate analgesic efficacy. Therefore, in order to achieve proper pain management in cancer patients, it is necessary to simultaneously minimize both the pain and the adverse effects of opioids employed for its control[12,36,39,40].

It is essential that health professionals assess the barriers that prevent or hinder the use of opioids in the elderly when treating cancer pain. In several situations, these patients are undertreated due to the lack of knowledge about cancer pain management, due to their pain complaints not being adequately taken into account, due to the fear of the complications arising from the use of opioids and due to bureaucratic and cultural difficulties in the implementation of this type of pharmacological therapy.

Some points are important to elucidate the difficulties in prescribing opioids when treating cancer pain, such as inadequate pain assessment, as only a small number of physicians reported applying pain management guidelines in their practice; 23 to 31% of physicians tend to delay the adoption of strong opioids until patients reach the terminal stage of their disease, or until their pain becomes intractable due to the difficulty in managing adverse effects; 25 to 40% of physicians are concerned about opioid addiction, and there is even greater fear in patients with a family history of addiction. Moreover, although oncologists have shown excellent basic knowledge about the use of opioids to treat cancer pain than physicians in other specialties, there is still a significant information deficit within their specialty[15,24,27,37,39,41].

From the patient's perspective, other potential barriers to the use of opioids may include lack of communication with

physicians, resulting in insufficient notification of symptoms; misconceptions about the pain drug due to the fear of adverse effects, dependence, tolerance, and reduced immunity; and fatalistic beliefs, i.e., if the pain is increasing, the idea of inevitable and uncontrollable progression of the disease is created. Patients with drug concerns and misconceptions have worse adherence to treatment. In addition, pain intensity is associated with a higher level of psychological distress, including depression, anxiety, hostility, and mood disorders. Therefore, there is a need for psychiatric and psychological follow-up to complement and increase the efficiency of pharmacological treatment[10,13,22,23].

Also, bureaucratic difficulties imposed on the prescription by government agencies, as well as on the access to these drugs and their price, were reported. Regulatory restrictions on opioid prescribing differ widely across countries. Thus, in developed countries, physicians have access to a wide range of opioids, while those in developing countries have limited treatment options[20-22].

In order to solve or alleviate these problems mentioned above, there are several strategies, including the use of validated pain scales for patient pain selection and monitoring; multicomorbidities assessment; multidimensional assessment; choice of opioids according to the particularities and pathophysiology of pain; anticipation and treatment of adverse effects; referral to other specialties when necessary; education of patients, families and, especially, caregivers; provision of psychosocial support; information to patients that most cancer pain can be alleviated; establish realistic and objective expectations regarding pain. In addition to this, it is necessary to promote educational lectures to disseminate strategies to be adopted for better pain management by health professionals and to increase the availability of opioids.

CONCLUSION

The results showed that opioids remain the pillar in cancer pain treatment in the elderly. They can be used for better pain management, but with caution due to the possible adverse effects. In addition, pain management in the elderly requires a multifactorial analysis, including comorbidities, polypharmacy, and patient functionality. Therefore, it is necessary to treat the elderly patient individually in order to maximize results, reduce adverse effects and improve quality of life.

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Joint mobilization associated or not to other therapies reduces chronic musculoskeletal pain: a systematic review

Mobilização articular associada ou não a outras terapias reduz dor musculoesquelética crônica: uma revisão sistemática

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ABSTRACT

BACKGROUND AND OBJECTIVES: Joint mobilization is a non-pharmacological technique used to treat chronic musculoskeletal pain. However, it is controversial due to a lack of studies comparing its effects on this painful condition. The objective of this study was to assess the risk of bias in clinical trials investigating the effect of joint mobilization on chronic musculoskeletal pain.

CONTENTS: A systematic search on Pubmed, Cochrane Library, ScienceDirect, Scielo, PEDro, CINAHL, SPORTDiscus, LILACS, BVS, PsycINFO, Web of Science, and Scopus was performed on September 2019 from the combination of three keywords: Musculoskeletal Manipulations AND Chronic Pain AND Musculoskeletal Pain. Randomized controlled clinical trials that evaluated the use of joint mobilization associated or not to other therapies in chronic musculoskeletal pain treatment were included. Five thousand five hundred eighty-seven articles were screened, and 14 studies were analyzed, including 812 participants, with a mean age of 54 years, and female being the most affected. According to these articles, joint mobilization promoted the reduction of pain intensity in short and long terms, increase in range of motion, strength and function when used alone or in association with conventional physiotherapy. Regarding methodological quality, most of the studies were classified with low risk for selection, performance, detection and reporting bias. In the "other bias" item, which considered therapists experience time and types of treatment applied, only one study presented low risk and other study presented an unclear risk.

CONCLUSION: Joint mobilization seems to be an effective technique for the treatment of chronic musculoskeletal pain. However, it is still necessary to investigate and compile studies with greater methodological quality, thus promoting greater support to evidence-based practice.

Keywords: Chronic pain, Musculoskeletal manipulations, Musculoskeletal pain.

RESUMO

JUSTIFICATIVA E OBJETIVOS: Mobilização articular é uma técnica não farmacológica usada no tratamento da dor musculoesquelética crônica. No entanto, é controverso devido à falta de estudos que comparem seus efeitos sobre essa condição de dor. O objetivo deste estudo foi avaliar o risco de viés em ensaios clínicos que investigam o efeito da mobilização articular na dor musculoesquelética crônica.

CONTEÚDO: Foi realizada uma busca sistematizada no Pubmed, Cochrane Library, ScienceDirect, Scielo, PEDro, CINAHL, SPORTDiscus, LILACS, BVS, PsycINFO, Web of Science e Scopus em setembro de 2019 com a combinação de três palavras-chave: Musculoskeletal Manipulations AND Chronic Pain AND Musculoskeletal Pain. Ensaios clínicos controlados e aleatorizados que avaliaram o uso de mobilização articular associada ou não a outras terapias no tratamento da dor musculoesquelética crônica foram incluídos. Foram encontrados 5587 artigos e analisados 14 estudos, incluindo 812 participantes, com idade média de 54 anos, sendo o sexo feminino o mais afetado. Nestes, a mobilização articular promoveu redução da dor em curto e longo prazo, amplitude de movimento, força e melhora da função quando utilizado isoladamente ou em associação à fisioterapia convencional. Em relação à qualidade metodológica, a maioria dos estudos foi classificada com baixo risco para seleção, desempenho, detecção e viés de relato. No item *"other bias"*, que considerou terapeutas com tempo de experiência e tipos de tratamento aplicados, apenas um estudo apresentou baixo risco e outro estudo apresentou risco incerto.

CONCLUSÃO: Mobilização articular parece ser uma técnica eficaz para o tratamento da dor musculoesquelética crônica. No entanto, é necessário realizar estudos com maior qualidade metodológica, promovendo maior apoio à prática baseada em evidências.

Descritores: Dor crônica, Dor musculoesquelética, Manipulações musculoesqueléticas.

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INTRODUCTION

Chronic musculoskeletal pain (CMP) is defined as a painful condition associated with dysfunction in muscles, ligaments, tendons, bones, and/or adjacent structures that lasts for more than three months[1,2]. Musculoskeletal conditions are the main cause of disability worldwide, with a prevalence ranging from 13.5 to 47% of the general population[3]. The main risk factors for this condition are advanced age, female sex, smoking, low schooling, sedentary lifestyle, poor social interaction, depression and anxiety[4].

This type of pain has a multifactorial etiology, which may have a definite cause (traumatic, ischemic, tumor, inflammatory, overload, overuse) or non-specific causes[5,6]. Several characteristics may be present in these patients, as generalized, diffuse and/or local muscle pain, physical and mental fatigue, a decrease of muscle strength, demotivation, sleep disorders, among others[6-8], which may lead to increased health costs and reduced quality of life[9].

The treatment of CMP can be performed by a multiprofessional team and consists of pharmacological and/or non-pharmacological therapies[10]. The most used drugs are analgesics, non-steroidal anti-inflammatories, antidepressants, neuroleptics, anticonvulsants and myorelaxants[11]. Some non-pharmacological therapies involve physiotherapeutic techniques such as acupuncture, kinesiotherapy, electrotherapy, thermotherapy, phototherapy, spinal manipulation and massage therapy which aim to reduce pain and improve the quality of life of these patients[2,12].

Currently, these non-pharmacological treatments are being prioritized because of the lower risk of adverse effects. Manual therapy (MT) is one of these non-pharmacological techniques most widely used in the treatment of dysfunctions affecting the musculoskeletal system. It consists of a physiotherapeutic treatment that includes therapeutic massage, joint mobilization (JM), manipulation, among others[2].

JM is a technique used to treat musculoskeletal pain in the axial and appendicular skeletons. It is indicated to reduce pain, muscle spasms, reversible joint hypomobility, positioning/subluxation failure, progressive limitation, and functional immobility[13]. However, this technique has limitations and/or contraindications that consist of irreversible hypomobility, joint effusion and inflammation. The neurophysiological and mechanical effects caused by the use of joint mobilizations provide analgesia in patients with CMP[13,14].

Studies suggest[13,15,16] that JM activates the dorsal area of periaqueductal gray matter (PAG) of the brain, and this influences on pain perception. Studies show an immediate reduction of pain and an increase in sympathetic nervous system activity, suggesting an indirect relationship with the dorsal area of PAG and association between increased stimulation of sympathetic nervous system and reduction of mechanical pain threshold[13,17-19]. An experimental study has shown an analgesic response accompanied by sympathetic nervous system activation after the electrical stimulation of the midbrain, originating in PAG[20]. Other clinical studies have shown a sympathetic-excitatory change combined with a hypoalgesic response after spinal JM, with increased skin conductance[21-29], respiratory and heart rate[30], and decreased skin temperature[31,32]. Changes in central sympathetic activity may be directly related to modulation response during therapeutic intervention[29] and it is also hypothesized that JM initiates the inhibitory mechanisms in the dorsal region of the PAG[13].

Using grade III JM in an experimental model of ankle joint inflammation, showed action through spinal blockade of serotonergic (5HT1) receptors, found in nucleus raphe magnus (NRM) and noradrenergic (alpha 2), located mainly in a small nucleus in the gray matter of the pons, the locus coeruleus. However, blockade of GABA or opioid receptors had no influence on the analgesic effect produced by joint mobilization[33]. These data may suggest that MA reduces CNS pain through non-opioid descending inhibitory pathways from the rostral ventromedial medulla and dorsolateral pontine tegmentum. More recently, the role of the nociceptive adenosinergic system has been shown to mediate the antihyperalgesic effect of MA by activating A1 adenosinergic receptors that predominantly mediate the effects of synaptic transmission in the superficial region of the dorsal horn[34].

There are several studies on the use of MT in diseases and other conditions, such as chronic spinal pain and osteoarthritis (OA)[10,13]. A recently published meta-analysis about manipulation and mobilization, specifically for the treatment of chronic low back pain, has shown that both therapies appear to be safe and that there is moderate quality in the studies that support the use of these techniques to reduce this type of pain[14].

Another meta-analysis addressed the use of manual therapy, exercise therapy (ET), or combined treatment for adults with cervicalgia. Quality of included studies was moderate and the authors concluded that combined treatment consisting of MT and ET does not appear to be more effective in reducing the intensity of resting neck pain, cervical spine disability, or quality of life improvement in adult patients with cervicalgia when compared to only ET[35].

Although it presents moderate scientific evidence according to the previously published studies, the use of JM in patients with CMP still presents controversies due to the lack of studies that directly compare its effects in this painful condition. Therefore, there is an even greater need for studies with methodological quality that is rigorous enough to indicate treatments in this area. Thus, in order to verify the existence of clinical trials related to this topic, this systematic review aimed to investigate and evaluate the effect of protocols for JM application associated or not to other therapies in the treatment of pain and motor performance in patients with CMP.

CONTENTS

As a PICO strategy, randomized trials with a control or placebo group that evaluated the use of JM associated or not with other therapies in CMP treatment were included in this review. The studies that presented participants older than 18 years old with chronic pain related to musculoskeletal dysfunction for time ≥3 months and who were treated with JM associated or not with other therapies were selected.

Clinical trials comparing any type of JM with placebo or sham intervention, with no other type of treatment, mobilization as an isolated therapy or in combination with other conservative thera-

pies have been included. Clinical trials comparing different protocols of JM (e.g., different degrees, series, repetitions, and/or body sites/segments) were also included.

The exclusion criteria were studies with participants who presented oncological pain, headache, temporomandibular dysfunction (TMD), other painful conditions. It was also excluded studies with patients who were undergone to other modalities of therapies and/or mobilization under anesthesia or performed by machines as forms of treatment, use of JM only outside the site of pain, studies that did not report how long considered the pain condition as chronic and cross-over clinical trials. Studies that had no full-text accessible, and that was not possible to contact the authors, were also excluded.

The primary outcomes evaluated were pain measured by a validated pain score scale, such as the visual analog scale (VAS) and numerical rating scale (NRS) and pressure pain threshold (PPT), measured by digital pressure algometer. As secondary outcomes were considered: the range of motion data (ROM) accessed through universal goniometer or inclinometer, muscle strength measured indirectly or directly through the isokinetic dynamometer and manual tests, functionality measured by validated functional tests, quality of life through validated questionnaires, such as SF-36 and QoL for general measures, adherence to treatment measured by the number of sessions that the individual performed and patient expectation /satisfaction measured through the patient's report and the Likert scale.

Protocol and register

This research protocol was registered in the International Registry of Systematic Reviews PROSPERO (CRD 42016046029). The inclusion criteria and analyses of studies were performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Cochrane Handbook for Systematic Reviews of Interventions.

Search strategy

The studies were screened in the following electronic databases: Pubmed, Cochrane Library, ScienceDirect, Scielo, PEDro, CINAHL, SPORTDiscus, LILACS, BVS, PsycINFO, Web of Science, Scopus and Google Scholar. There were no restrictions on language or year of publication. The search was performed in September 2019 by combining the following descriptors: Manual Therapy/ Musculoskeletal Manipulations ("Musculoskeletal Manipulations"[mesh terms] OR (manipulations, musculoskeletal) OR (manual therapies) OR (manual therapy) OR (therapies, manual) OR (therapy, manual) OR (manipulation therapy) OR (manipulation therapies) OR (therapies, manipulation) OR (manipulative therapies) OR (manipulative therapy) OR (therapies, manipulative) OR (therapy, manipulative) OR (therapy, manipulation)), Chronic Pain ("Chronic Pain"[mesh terms] OR (Chronic Pains) OR (Pains, Chronic) OR (Pain, Chronic) OR (Widespread Chronic Pain) OR (Chronic Pain, Widespread) OR (Chronic Pains, Widespread); (Pain, Widespread Chronic) OR (Pains, Widespread Chronic) OR (Widespread Chronic Pains)) e Musculoskeletal Pain ("Musculoskeletal Pain"[mesh terms] OR (Musculoskeletal Pains) OR (Pain, Musculoskeletal) OR (Pains, Musculoskeletal)).

Searches were remade immediately before the final analyses and additional studies were retrieved for inclusion. The reference lists of all primary studies were checked, and all articles were revised for additional references. Data collection and analyses were performed in accordance with the methods set out in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Cochrane Handbook for Systematic Reviews of Interventions.

Data selection and extraction

Two authors independently extracted data from all studies included using an Excel spreadsheet. This worksheet included extracting information about characteristics of studies, participants, methodological aspects, interventions, comparisons, primary and secondary outcomes, results, chronic pain condition, mobilization type, and association with other interventions. At this stage of the study, disagreements among reviewers were discussed with a third investigator.

Quality assessment

The risk of bias was assessed using the Cochrane Collaboration tool by two reviewers independently. Thus, six domains were evaluated: selection bias (random sequence generation and allocation concealment), performance bias (participants blinding), detection bias (evaluators blinding), attrition bias (results with incomplete data), reporting bias (selective reporting of outcomes) and other biases. For the judgment of this last type of bias (Other bias) the following aspects were considered: the number of physiotherapists who applied the protocols and their years of experience in the area (over one year), mobilization type (with different characteristics and/or combination with other therapies, presence of control group), no validated placebo for mobilization; compared with different therapies and with different application objectives.

Each of these biases was classified as low risk, high risk, or unclear risk. Review Manager 5.3 was used for all quantitative analyses. The searches were remade immediately before the final analyses in September 2019 and additional studies were retrieved for inclusion in order to ensure the selection of the largest possible number of studies.

Included studies

The database search recovered 5587 potentially relevant references: Pubmed (258), PEDro (28), CINAHL (32), Cochrane Library (39), LILACS (0), Scielo (2), ScienceDirect (4412), Scopus (343), SPORTDiscus (19), Web of Science (145), PsycINFO (15), BVS (194) e Google Scholar (100). The search retrieved 5587 records of trials after removal duplicates, of which 30 articles were selected for full-text evaluation and 11 clinical trials met the inclusion criteria. Hand search on the reference lists of all primary studies was performed and further three clinical trials were selected; thus, 14 clinical trials were included for qualitative synthesis. Figure 1 shows the flowchart of the search and selection process in this review.

Included clinical trials examining the JM intervention associated or not with other therapies in the treatment of CMP were publi-

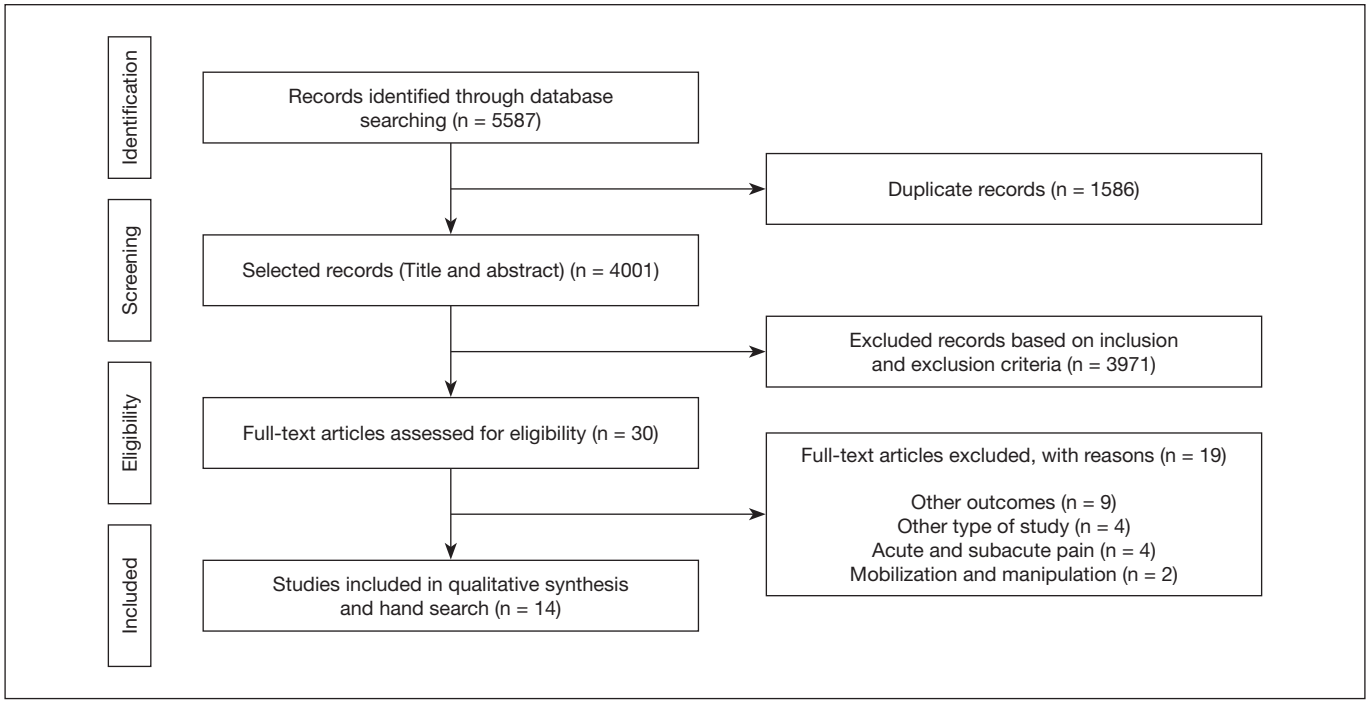

Figure 1. Flow of the studies through the review

shed between 2008 and 2018. The total sample from 14 studies was 812 participants, ranging from 28 to 120 participants in each study. Of these, eleven (n=11) performed the sample calculation to estimate the number of subjects included[36-46]. The mean age of participants was approximately 54 years, ranging from 18 to 90 years. On average, a higher number of female participants were found (60,98%).

Some studies (25%) considered chronic pain after three months. Of these, two were about cervicalgias[41,42] and one about rotator cuff injuries[36]. Two studies (16,66%) had as inclusion criteria patients with pain for more than 10 years[44,47]. In another study (8,33%), chronic epicondylitis as of six months were considered for inclusion[15]. Table 1 summarizes the characteristics of the included studies.

Table 1. Characteristics of the included studies

Authors	Sample	Chronic pain condition	Interventions description	Control Description	Outcomes	Instruments	Results	Conclusion
Bennell et al.[36]	Total (n=120) (experimental group - EG, (n=59), and control group - CG (n=61)); 22 weeks follow-up (EG n=59 and CG n=61)	Chronic injury of the rotator cuff	Soft tissue massage; glenohumeral JM (anteroposterior and inferior sliding); Thoracic and cervical mobilization (grade IV); scapular rehabilitation; postural taping shoulder and scapula; home exercises	Placebo ultrasound, light application of non-therapeutic gel on the shoulder	Shoulder pain and disability; pain intensity at rest and movement; global perception; quality of life; shoulder isometric strength; adherence to treatment	SPADI; NS; Likert Scale; SF-36 e AQoL; Nicholas Manual Muscle tester; Records of the number of physical therapy visits	There was no difference between groups on pain and disability of shoulder, on pain at rest and movement, both groups showed significant improvement; the participants in active group showed greater satisfaction with treatment, despite non-significant difference between groups. The active group showed a significant improvement in SPADI than placebo group after 22 weeks, although there was no difference between groups for pain reduction or percentage of participants who reported treatment success. The active group obtained better muscle strength, less interference in activities and better quality of life	A standardized program of manual therapy and home exercises did not present immediate benefits for pain and function compared to a placebo group. However, greater improvements were observed in shoulder function and strength at 22-week follow-up, suggesting that benefits with active treatment take time to manifest

Continue...

Table 1. Characteristics of the included studies – continuation

Authors	Sample	Chronic pain condition	Interventions description	Control Description	Outcomes	Instruments	Results	Conclusion
Beselga et al.[38]	Total (n=40) EG n=20 and CG n=20	Hip OA	JM with flexion and internal hip rotation (Mulligan technique)	Simulated therapy of mobilization technique with hip movement	Pain intensity at rest; ROM of hip flexion and internal rotation; functionality.	NS; Universal goniometer; Timed up and go test; 30s Chair Stand; SPWT	In the EG, there was pain intensity reduction, increased hip flexion and internal rotation, and functional tests also improved with a relevant clinical effect. There were no significant changes in any outcome in CG	Pain intensity, hip flexion ROM and physical performance improve immediately after the application of JM with movement in patients with hip OA. The immediate changes observed were clinically relevant.
Crossley et al.[39]	Total (n=92) (experimental group EG (n=39) and CG (n=42); 9 months follow-up EG (n=35) and CG (n=34))	Patellofemoral OA	Functional recovery and strengthening exercises for quadriceps and hip muscles; patellar bandage; patellofemoral, tibiofemoral JM (without specifications) and soft tissue; education in OA	Education in OA	Global perception; Movement pain intensity; Activities of daily living; Adverse events and use of drugs	Likert scale; VAS; KOOS-ADL; Physiotherapy attendance, home exercises, description of adverse events and the medicines used	The EG reported a higher percentage of the item "greater improvement" of the general clinical signs on the Likert scale and greater reduction of pain when compared to CG. There was no significant effect on ADLs. After 9 months, there was no significant effect on self-reported pain	After 3 months of treatment, the EG presented a superior result in global perception of clinical change and pain when compared to CG. However, after 6 months, there was no maintenance of the effects observed previously either in physical function and/or other positive effects.
Farooq et al.[42]	Total (n=68) EG (n=34) and CG (n=34)	Chronic neck pain	Physiotherapy (Infrared, TUS, TENS, isometric exercises for neck); Cervical mobilization (Maitland posteroanterior oscillatory mobilization), participant education, home exercises	Physiotherapy participant education, home exercises	Cervical pain intensity at rest; Neck disability level; Cervical ROM; cervical muscular endurance; Analgesic intake during treatment	VAS; NDI; Universal goniometer; Muscle endurance tests	There was a greater significant reduction of pain and disability in EG when compared to control group, as well as an increase in the resistance of cervical muscles and cervical ROM compared with CG. All outcomes had significant improvement in both groups. However, a larger increase was observed in the EG.	The combination of cervical mobilization with physical therapy is more effective in reducing pain, disability, muscular resistance and ROM in patients with chronic mechanical neck pain compared to the group treated only with physiotherapy
Horst et al.[48]	Total (n=72) EG (n=36) and CG (n=36; 3 months follow-up EG (n=33) and CG (n=33)	Frozen Shoulder	Activity-oriented therapy (strengthening of shoulder muscles, several verbal commands for specific movements of the shoulder and scapula), aerobic training, cryotherapy, laser therapy and exercise with elastic bands	Structural oriented therapy (PNF, verbal feedback, passive anteroposterior humerus and scapula JM, separation training and joint approach), aerobic training, cryotherapy, laser therapy and exercise with elastic bands	Pain intensity at rest; Upper limbs functionality; ROM; Muscle strength	McGill Pain Questionnaire; Upper Extremity Motor Activity Log modified; Goniometer; Daniels and Worthingham muscle test	The activity-oriented group achieved significant increases in functional performance and activities of daily living compared to control group after 10 days of therapy and in the follow-up of three months	An activity-oriented therapy program has longer benefits than targeted structural therapy
Mayor et al.[43]	Total (n=90) EG (n=45) and CG (n= 42)	Mechanical neck pain	Manual therapy (cervical mobilizations (technique site not specified), neuromuscular techniques, stretches and invasive treatments of trigger points), home exercises and postural guidelines	TENS (F: 80 Hz, T: ≤ 150 µs, adjustable intensity), home exercises and postural guidelines	Pain intensity at rest; Neck disability level; Quality of life; Depression and anxiety; Drug use (active principle and periodicity); Expectation of treatment; Adverse events	VAS; NDI; SF-12; GHQ-28; Records (drugs prescribed by physicians, periodicity of consumption, adherence to recommended postural care and recommended exercise)	There was a significant difference in reduction of pain intensity in both groups	Treatment with TENS and manual therapy produces a significant reduction in pain intensity, and there are no differences between these treatment groups

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Table 1. Characteristics of the included studies – continuation

Authors	Sample	Chronic pain condition	Interventions description	Control Description	Outcomes	Instruments	Results	Conclusion
Richer, Marchand and Descarreaux[15]	Total (n=37) EG (n=19) and CG (n=18), 3 months follow-up EG (n=15) and CG (n=12)	Chronic lateral epicondylitis	Anteroposterior elbow mobilization (Mill manipulation described by James Cyriax), cryostimulation with cryospray at the trigger point	Ischemic pressure at the myofascial trigger point	Pain intensity at rest; gripping force without pain; functional outcomes (disability and pain)	VAS; Hand dynamometer; PRTEE	Significant reduction of pain and functional index were observed in both groups post intervention evaluation and were maintained at follow-up.	Based on preliminary data from this study, the combination of cryostimulation treatment and manual therapy does not provide short- and long-term benefits. The manual myofascial point treatment and mobilization techniques provided positive results in chronic lateral epicondylitis.
Shashua et al.[40]	Total (n=50) EG (n=25) and CG (n=25); 6 months follow-up EG (n=23) and CG (n=23)	Plantar fasciitis	TUS, stretching and anteroposterior talocrural JM	TUS and stretching	Pain intensity at rest; Dorsiflexion ROM; Lower limbs functionality; PPT	NS; Inclinometer; LEFS; Pressure algometer	No significant differences were found between groups in any outcome. Both groups showed a difference in pain intensity and lower limb function. Both groups increased dorsiflexion ROM, but there was no difference between groups	The addition of ankle and foot JM with the aim of improving dorsiflexion ROM is no more effective than the TUS treatment and stretching only. The association between limitation of dorsiflexion and plantar fasciitis probably occurs because of soft tissue limitation and not from the joint
Snodgrass et al.[41]	Total (n=64) EG high force mobilization (n=21), low force mobilization (n=22), CG (n=21); 4 days follow-up EG: high force mobilization (n=20) and low force mobilization (n=22), CG (n=20)	Neck pain	Postero-anterior JM (grade III) in cervical spine C7 vertebra with force of 30 N or 90 N	Laser treatment turned off	PPT (spinous process of the cervical vertebra, upper trapezius muscle right, median right nerve trunk in the elbow); Pain intensity at rest; Cervical ROM; Cervical stiffness; Neck disability level	Algometer; VAS; Cervical ROM instrument; Custom device; NDI	At follow-up, the 90 N group had lower pain than 30 N group and lower cervical stiffness than the control group. There was no significant difference between the groups in LDP and WMD after treatment or at follow-up	A specific dose of JM in terms of applied force seems necessary to reduce stiffness and potentially pain in patients with chronic neck pain. The changes were not observed immediately after the mobilization, suggesting that their effects are not directly mechanical
Sterling et al.[49]	Total (n=34) EG (n=19) and CG (n=15)	Chronic whiplash associated disorders	Cervical lateral glide at the C5-C6 level	Manual contact	Pain and disability in cervical spine; Emotional distress; Pressure pain threshold; Thermal pain threshold; NFR; pain associated to NFR test	NDI; GHQ-28; Algometer; Thermotest system; EMG; VAS		Manual cervical lateral glide technique has the ability to modulate spinal hyperexcitability in patients with chronic whiplash injury in short term. However, manual cervical lateral glide is not recommended until its long-term effects are discovered and whether they are equivalent to reduced pain and cervical inability
Tavares et al.[37]	Total (n=60) EG (n=20), placebo group (n=20), and CG (n=20)	Chronic low back pain	Posteroanterior central JM grade II (for 30 seconds on each lumbar vertebra L5 to S1)	Placebo: reproduced the same positioning of the hands used in the EG without rhythmic oscillations and with the hands at rest; CG: without intervention	Pain intensity at rest; Low back pain-related incapacity; Pain-related catastrophi-zing	NS; ODI; PCS		JM was effective in improving disability, pain intensity and pre and post-intervention catastrophizing. In comparison of the effects between intervention groups, a reduction on pain intensity was observed in mobilization and placebo groups in relation to CG, suggesting a placebo effect associated to mobilization

Continue...

Table 1. Characteristics of the included studies – continuation

Authors	Sample	Chronic pain condition	Interventions description	Control Description	Outcomes	Instruments	Results	Conclusion
Villafañe et al.[45]	Total (n=29) EG (n=18) and CG (n=18; 1 week follow-up EG (n=14) and CG (n=15); 2 weeks follow-up EG (n=14) and CG (n=15)	Secondary thumb carpometacarpal OA	Grade III Kaltenborn JM (anteroposterior glide with carpometacarpal joint traction)	TUS in non-therapeutic doses	Pressure pain threshold; Pinch and grip force	Algometer; Pinch dynamometer, Hand dynamometer		Kaltenborn JM reduced pain in carpometacarpal joint and the scaphoid bone area. Thus, mobilization can be effective in reducing pain and potentially improving function in OA
Villafañe et al.[44]	Total (n=28) EG (n=14) and CG (n=14); 1 week follow-up (EG (n=14) and CG (n=14); 2 weeks follow-up EG (n=14) and CG (n=14)	Thumb carpometacarpal OA	Maitland postero-anterior trapeziometacarpal JM	TUS in non-therapeutic doses	PPT Pinch and grip strength. * in the symptomatic limb	Algometer; Pinch dynamometer, Hand dynamometer		Accessory passive mobilization increases PPT at carpometacarpal joint of thumb. However, therapy does not increase motor function in patients with thumb carpometacarpal OA
Villafañe et al.[47]	Total (n=28) EG (n=14) and CG (n=14); 1 week follow-up EG (n=14) and CG (n=14); 2 weeks follow-up EG (n=14) and CG (n=14)	Thumb carpometacarpal OA	Carpometacarpal JM with anteroposterior slide	Simulated technique and TUS in thumb region	PPT in carpometacarpal joint, in scaphoid and hamato bones; Pinch and grip force; *asymptomatic limb	Algometer; Pinch dynamometer, Hand dynamometer		The application of unilateral accessory passive mobilization directed to the symptomatic carpometacarpal joint provided an increase in PPT 2 weeks after treatment; however, the differences were small and of limited clinical value. No contralateral motor effects were observed

SPADI = Shoulder Pain and Disability Index; NS = Numeric Scale; SF-36 = Medical Outcomes Study 36-item short form; AQoL = Assessment of Quality of Life; TUG test = Time Up and Go test; SPWT = Self Placed Walk test; OA = Osteoarthritis; TENS = Transcutaneous Electrical Nerve Stimulation; TUS = Therapeutic Ultrasound; ROM = Range of Motion; VAS = Visual Analog Scale; JM = Joint Mobilization; KOSS-ADL = Activities of Dailu Living subscale of the Knee Injury and Osteoarthritis Outcome Score; NDI = Neck Disability Index; PNF = Proprioceptive Neuromuscular Facilitation; SF-12 = Health Questionnaire SF-12; GHQ-28 = Goldberg Depression and Anxiety Scale; LEFS = Lower Extremity Functional Scale; PRTEE = Patient Rated Tennis Elbow Evaluation; PPT = Pressure Pain Threshold; EMG = Electromyography; CHQ-28 = General Health Questionnaire 28; PCS = Pain Catastrophizing Scale; ODI = Oswestry Disability Index; EG = experimental group; CG = control group; ADL = activities of daily living; NFR = nociceptive flexion reflex.

PRIMARY OUTCOMES

Pain intensity

The majority of included trials (11 of 14) measured pain intensity only at rest[15,36,38-45,48]. One study measured the intensity of pain during movement (39), and one study evaluated pain intensity on movement and at rest[36]. Five studies evaluated the intensity of pain through the visual analog scale (VAS)[15,39,41-43] and other four studies used the numerical rating scale (NRS)[36,38-40]. One study evaluated pain through the McGill Pain Questionnaire[48]. In study[49] VAS was used to evaluate pain intensity associated with nociceptive flexion reflex test[49].

All studies have shown significant short- and/or long-term reduction of pain intensity following JM combined or not with other therapies[15,36,38-45,48].

Pressure pain threshold (PPT)

Some studies have evaluated PPT as a primary outcome[40,41,44,46,47,49]. This variable was measured through a digital pressure algometer at different points, according to pain location. The study[49] evaluated PPT in patients with chronic cervical disorders related to whiplash injury. Three measurements were conducted in the C6 spinous process at the median nerve trunk bilaterally elbow and the tibialis anterior muscles bilaterally at two times before and after therapy[49].

The study[46] collected the measurements of PPT in the carpometacarpal joint at the bottom of the anatomical snuffbox and tubercle of the scaphoid bone. Three measurements were performed in the dominant hand of subjects with a one-minute interval, four times before treatment, 5 minutes after the treatment, 1 and 2 weeks after therapy.

On study[44] the PPT was measured three times, with a rest interval of one minute between measurements, in bones connected to trapeziometacarpal joint, of scaphoid bone apophysis and hamato bone in four moments (baseline, immediately after treatment, one and two weeks after treatment) on symptomatic hand with OA carpometacarpal.

Another study[47] consisted of a secondary analysis that focused on the contralateral hand (asymptomatic). The PPT was evaluated three times with a rest interval of one minute between measurements on the carpometacarpal joint of the contralateral thumb and the symptomatic hand with carpometacarpal OA, on scaphoid bone tubercle and hamato bone process in four moments (baseline, immediately after treatment, one and two weeks after treatment).

On study[41] PPT measurements were performed three times, with an interval of 10 seconds between measurements in the following points: close to spinous process of cervical spine at medullary level treated on right side, with participant in pronated position, upper right trapezius muscle, between C7 and acromion, with sitting participant and trunk of the right median nerve at the

elbow, medial to the biceps tendon, with the elbow at approximately 30° flexion, with forearm resting on a support and participant sitting in three moments (before, after and follow-up).
The study[40] performed three PPT measurements with a 30-second interval between each application at the pain site in patients with plantar fasciitis. Algometry was measured twice (baseline and at the end of all care sessions).
Five of six studies[40,41,44-46] demonstrated a significant increase in short and/or long-term pressure pain threshold after JM application, associated or not with other therapies. Only one study[49] showed no significant difference after the use of this therapy.

SECONDARY OUTCOMES

Range of motion

Five of the included studies performed ROM measurement[38,40-42,48]. Among studies that evaluated ROM with a universal goniometer, one article evaluated only active mobility[42], and two other studies did not specified[38,48]. Active ROM was still evaluated through the inclinometer in a study[40] and through the cervical range of motion instrument[41].
Four articles showed a significant increase of ROM at cervical[42], shoulder[48], hip[38], and foot[40] joints after JM application associated or not with other therapies. One study[41] did not find any significant difference for cervical ROM after therapy.

Muscle strength

Five studies evaluated muscle strength[15,36,44,46-48]. In the study[36], the isometric strength of the symptomatic shoulder was assessed for abduction, internal and external rotation through the Nicholas Manual Muscle Tester (Lafayette, EUA) performed with a dynamometer. After the demonstration and training test, participants were asked to push as much as possible against the dynamometer for 4 seconds while the evaluator provided a verbal stimulus[36].
The study[48] used muscle testing procedures by Daniels and Worthingham to assess the strength of the major shoulder muscles. In this system, muscle strength is marked with a numerical rating ranging from zero, indicating no muscle activation, to 5 for the best possible response to manual resistance in a reduced range of the muscle group that performs the movement.
Other studies[15,44,46,47] used the hand dynamometer to measure the strength of patients with chronic lateral epicondylitis and thumb metacarpal OA, respectively[15,44,46,47]. The studies from[44,46,47] also used the tweezer dynamometer to evaluate thumb strength[44,46,47].
Increased muscle strength after JM application associated or not to other therapies was observed in three studies[36,46,48]. Three other studies found no changes in strength after therapy[15,44,47].

Functionality

Ten studies that were included investigated hip, shoulder, knee, and foot functionality. Nine of them used questionnaires[36,37,39-43,48,49] and one used functional tests[38], all with validation.
The study[38] on the immediate effects of mobilization in patients with hip OA was the only that evaluated the functional indexes of patients through validated tests[38]. The Timed Up and Go test (TUG), which simulates some functional activities of daily living (from sitting to standing, walking and standing to sitting) [38]; the 30s Chair Stand Test (CST), which assesses function and strength of the lower limbs[38] and the 40m Self Placed Walk Test (SPWT), which measures the time required to walk on short distances[38].
The other studies used the following questionnaires: Shoulder Pain and Disability Index (SPADI) to evaluate shoulder function in patients with chronic rotator cuff lesions[36]; Knee Injury and Osteoarthritis Outcome Score (KOOS) to evaluate knee function/performance in activities of daily living (ADL) in patients with patellofemoral OA[39]; the Neck Disability Index (NDI) was used to assess pain and disability of cervical spine in patients with chronic neck pain, cervicalgia and chronic whiplash injury disorders, respectively[41-43,49]; the Upper Extremity Motor Activity Log Modified to measure upper limb functionality in patients with frozen shoulder[48]; the Lower Extremity Functional Scale (LEFS) for assessing the functionality of lower limbs of patients with plantar fasciitis[40]; the Oswestry Disability Index (ODI) that was used in patients with chronic low back pain to measure pain-related disability in the lumbar spine[37] and the Patient Rated Tennis Elbow Evaluation (PRTEE), which evaluated the functional outcomes related to pain and disability in patients with chronic lateral epicondylitis[15].
Improvement of functionality was observed in seven studies[36-38,40-42,48] after JM application associated or not with other therapies. There was no significant difference in functionality in three studies[39,43,49] after JM application.

Quality of life

Three studies assessed quality of life (AQoL)[36,39,43], using different instruments, such as the Medical Outcomes Study 36-item short-form (SF-36)[36], the Assessment of Quality of Life (AQoL)[36], the ADL subscale of Knee injury and Osteoarthritis Outcome Score (KOOS)[39] and the 12-item health survey (SF-12)[43].
Only one study[36] showed a significant increase in the quality of life parameters after JM application. Two studies[39-43] did not show any significant difference in this outcome after therapy.

Adherence to treatment

Only two studies evaluated adherence of participants through medical records, considering the number of visits performed and the total number of visits that were pre-established in the study protocol[36,39]. Both studies showed good patient adherence to JM treatment, but no significant difference was observed between treatment and control groups.

Expectation/satisfaction

Three studies evaluated the expectations before the intervention, relating to their respective satisfactions after intervention[36,39,43]
A five-point Likert scale was used (1 = much worse, 2 = slightly worse, 3 = no change, 4 = slightly better, 5 = much better)[36,39], this data was registered in each patient's medical records. The study[43] evaluated the expectation before treatment from the concepts chosen by the patient: complete recovery, great improvement, partial relief or no expectation of relief. All three studies reported that most participants reported satisfaction and improvement with JM treatment performed.

Adverse events

Only three studies reported adverse events[36,39,43]. In the study[43],16.3% of patients treated with transcutaneous electrical nerve stimulation (TENS) (n=7) and 6.4% of those treated with manual therapy (n=3) reported treatment-related adverse effects. Three of them presented increased pain in the treated area and one showed the general physical condition of the group treated with TENS. Of those who received manual therapy, one patient reported clinical worsening during the first few days and the others did not specify symptoms[43].

Study[36] reported that during the intervention period, 17 participants out of 55 (31%) from the active group had adverse effects that included increased short-term pain during or after treatment (n=3), increase in short-term pain with home workouts (n=12) and slight irritation to tape used for postural taping (n=2). In the placebo group, five participants out of 61 (8%) reported adverse events involving increased short-term pain during or after treatment. During the follow-up period, 7 of 49 patients (14%) from the active group reported adverse events and included increased short-term pain with home exercise[36].

In the study[39] adverse events were observed in seven participants who undergone exercise, education, manual therapy, taping intervention (skin reaction to the use of tape (n = 2)); edema after treatment (n = 2); pain in other areas after exercise (lumbar n =1; ankle n=1; another knee n=1). All adverse events were mild, with no need for medical intervention or treatment discontinuation (some bandage adjustments were performed and/or exercises were done by the physiotherapist).

Thus, most of the adverse effects caused slight damages to the patients in included studies, were generally related to the increase of local pain immediately after the technique application, but without lasting for a long time.

Other variables

All studies recorded demographic data (sex, age, body mass index, height, among others). Other variables were also considered in some studies, such as thermal pain threshold[49], nociceptive flexion reflex and pain related to this test[49], pain catastrophizing[37], level of anxiety, and depression[43,49] and use of drugs during treatment[39,42,43]. Two studies evaluated the levels of depression and anxiety in the participants through the Goldberg Depression and Anxiety Scale (GHQ-28). In one study, it was evidenced that 42.6% of the participants treated with manual therapy presented anxiety and depression[43], and the other study showed that all individuals had high levels of anxiety and depression[49].

The study[49] evaluated the thermal threshold, nociceptive flexion reflex and the pain associated with this test and showed that there was an increase in the nociceptive reflex flexion threshold in the group treated with JM and that there was no significant difference in pain during the reflex test nociceptive flexion and at the threshold of thermal pain. On sutdy[37] catastrophizing evaluation of patients with chronic low back pain was performed and pain catastrophizing interference was observed in the treatment of these patients

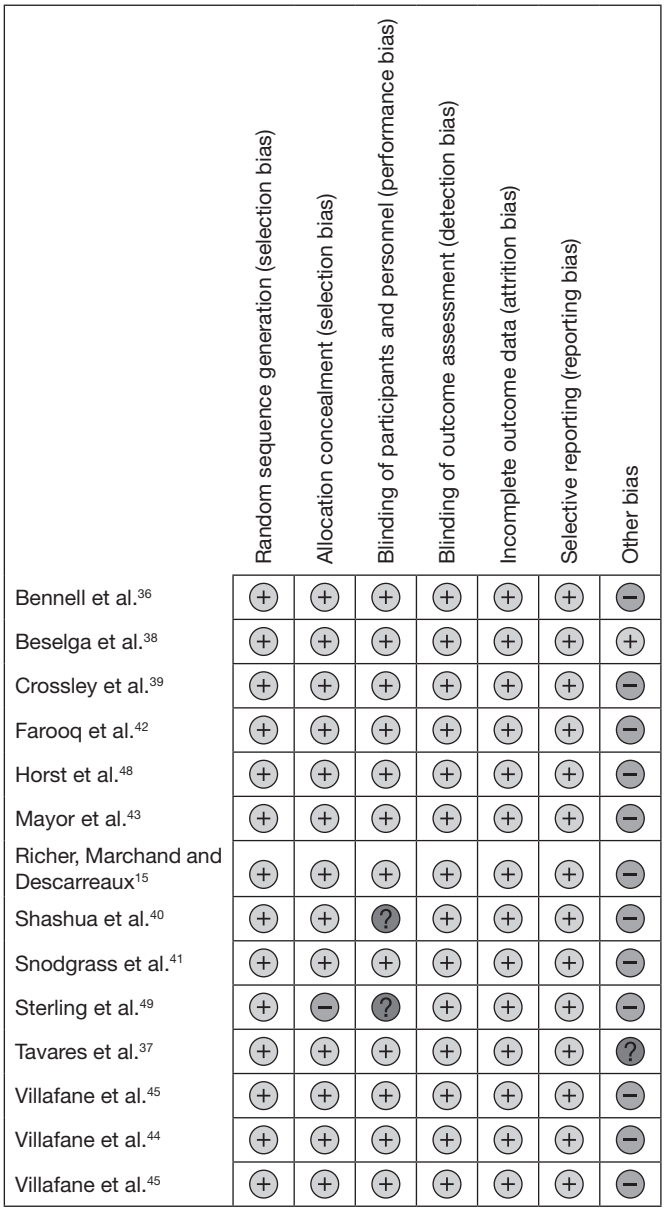
Three studies reported the use of drugs during treatment[39,42,43]. The study[39] evidenced similar use of analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), glucosamines, and fish oil. The study[42] use of pain medication was registered in five patients of both groups, and there was no significant difference between them. The study[43] details the periodicity of the consumption of NSAIDs, analgesics and muscle relaxants. In the group treated with manual therapy, 4.3% of patients took these drugs every day, while 12.8% reported weekly or monthly consumption.

Risk of bias

The studies were evaluated for the risk of bias (low, high, or unclear) in relation to six domains. Figure 2 summarizes the results of individual studies.

One study adequately described all domains and was considered as a low risk of bias[38]. One study presented a high risk for the selection bias by using an open randomization process (random list of numbers)[49]. Two studies presented an unclear risk for the performance bias because they did not present information about

Figure 2. Risk of bias



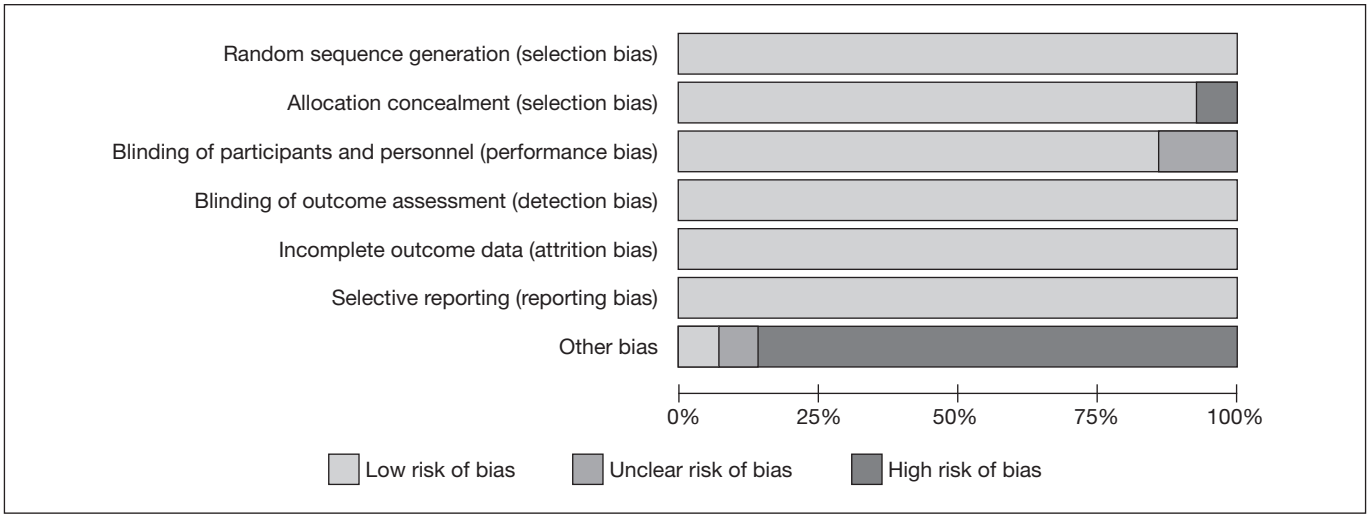


Figure 3. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies

the blindness of participants and researchers[40,49]. All studies had a low risk of reporting bias[15,36-44,46-49].

In the domain "other bias," 12 studies presented a high risk of bias[15,36,39-46,48,49]. Six reported that more than one therapist performed the mobilization[15,36,39,40,43,48], seven performed different types and techniques of JM without specifying the type of mobilization and/or combined with other therapies[15,36,39,40,42,43,48], and 11 articles used different treatment controls, such as TENS, therapeutic ultrasound, laser, stretching or patient education[15,36,39-44,47-49]. Three studies did not report the experience of the therapists who performed treatments[37,46,49]. One study was considered to be at an unclear risk because it did not report the number of therapists who performed the mobilization techniques and the time of clinical experience in the area[37].

In general, the methodological quality of studies was considered a low risk of bias. The values referring to the percentage of articles classified in each degree of risk of bias are represented in figure 3.

DISCUSSION

According to the studies analyzed, JM seems to have better results in the management of chronic musculoskeletal conditions when it was used alone or in combination with conventional physiotherapy. From the 14 articles included, seven used JM interventions alone compared to a control group using simulated placebo therapy[37,38], other interventions with appliances switched off or in non-therapeutic doses[41,44,46,47], manual contact[49] or without treatment[37] and seven used JM in association with therapeutic resources used in conventional physiotherapy (TENS, TUS, strengthening, patient education and home exercises) compared to the same therapy without JM[15,36,39,40,42,43,48]. This shows the scarcity of clinical trials that use only JM as treatment, which makes it difficult to know the efficacy of this technique alone in various types of musculoskeletal disorders. In addition, the lack of validated placebo techniques for JM also difficult the discovery of new evidence about technique effect.

For primary outcomes (pain intensity and pressure pain threshold), JM promoted short-term[37,38,44,46,47] and long-term[41] pain reduction in different types of musculoskeletal pain when only mobilization was used as treatment. When applied in combination with other therapies in musculoskeletal lower limb dysfunctions (patellofemoral OA and plantar fasciitis) and spine (chronic neck pain chronic disorders related to whiplash injury and chronic low back pain), the studies showed a reduction of pain after treatment[37,39,40,42,43,49]. In upper limb dysfunctions (rotator cuff injury, frozen shoulder, lateral epicondylitis and thumb carpometacarpal OA), some studies have reported pain reduction[15,46], and others did not observe any differences between groups[36,42,43,48]. Most of the articles also showed improvement of ROM, strength and function after JM treatment[15,36-38,40-42,46]. Based on these studies, most of them with good methodological quality, JM can be considered an effective therapeutic resource in reducing pain and improving the functionality of patients with CMP. There is insufficient evidence to determine the effect of JM on quality of life, adherence and patient expectancy in the treatment of CMP.

Previous reviews and meta-analyses show chronic musculoskeletal conditions studied separately and involving manual therapy as a set or combination of manual techniques (neck pain[35,50], lower back pain[14,51], patellofemoral pain[52], impingement syndrome[53], hip OA[1], or using a particular technique of JM for pain treatment[54]. In addition, it presents restrictions on language and publication period of selected articles, and the search was performed in a small number of databases, which makes these studies limited. Differently, the present review performed the search on 12 databases, without year and publication language restrictions, which reduces the risk of loss of some article at screening and, consequently, provides greater access to the data extracted from studies already published about this theme.

The prevalence of common musculoskeletal conditions has a strong relationship with age, being directly proportional to aging, with an increase of painful complaints due to the wear of the musculoskeletal system[3]. In this review, neck pain was more prevalent among included studies[41-43,40], in contrast to the number of back

pain studies in the literature, who had only one study included[37]. This may have been caused by not meeting the inclusion criteria in this review or the fact that manipulation seems to be the most appropriate technique for low back pain according to current revisions[14]. Later appear the injuries that affect the shoulders, such as rotator cuff disease[36] and frozen shoulder[48] and to a less extent, diseases such as lateral epicondylagia[15] and plantar fasciitis[40]. OA is a common condition shown in studies in different body regions and patellofemoral[17], carpometacarpal[44-46] and hip[16].

Autors[51] in a systematic review (SR) about JM and exercise efficacy for different stages of non-specific low back pain, found that JM (being the high speed and low amplitude manipulation of the pelvic loin region that presents evidence of moderate support compared to mobilization and soft tissue techniques including "myofascial," "miotensive" or "harmonic" techniques in this same body region), in combination with specific and/or general exercises, or usual medical care, are better than any of these isolated interventions.

In agreement, study[14] in a meta-analysis on manipulation and mobilization in the treatment of chronic low back pain, have observed that the manipulation of high speed and low amplitude (thrust) is the most recommended. However, the search conducted in this SR showed year restriction (January 2000 to April 2013), language (only articles in English), and a few electronic databases (Medline, Cochrane Register of Controlled Trials, PEDro, CINAHL, PsycINFO, and ICL). In this meta-analysis, a specific population was not defined since there was no homogeneity in the causes of low back pain, which implies a greater heterogeneity of studies and consequently a higher methodological bias and less applicability of these data in clinical practice.

In an SR about the use of exercise in mechanical neck pain, study[55] concluded that there was no evidence of high quality, indicating that there is still uncertainty about the efficacy of specific strengthening and resistance exercises for neck pain. Study[50], in SR about JM efficacy and exercise for nonspecific cervical pain, emphasized the importance of performing combined treatment (JM plus exercises), being better compared to JM or exercises alone.

The authors also showed that JM does not need to be applied at the symptomatic level to improve pain and can then be applied at adjacent levels according to the irritability status[50]. These reviews also show that manipulation is less indicated in cervical disorders, recommending that the thoracic manipulation or mobilization should be performed. This agrees with results found in studies included in this SR[41-43,49], who considered mobilization as a treatment with good results in patients with nonspecific mechanical neck pain and with whiplash injury-related cervical disorders, applied either alone or in association with conventional therapy.

In studies about chronic pain, pain intensity is considered the primary outcome in most clinical trials[56] and should be investigated both at rest and during movement. From the included studies, 12 evaluated only pain at rest[15,37,38,40-46,49], one study assessed only pain in motion[39], and only one has evaluated pain at rest and during movement[36]. Both the intensity of pain in rest and during movement must be evaluated because there are pain conditions that do not occur or have lower intensity at rest, which may mask the evaluation and generate a bias in the study. Therefore, it is very important to perform pain assessment in these two conditions in order to have more reliable data about the pain of a population.

In the reviews cited above, positive results were also observed for the reduction of pain associated with the use of manual therapy/mobilization and combinations with exercises[50]. In a previous SR about the use of physiotherapeutic treatment in subacromial pain, it has been shown that exercise therapy should be the best treatment for pain reduction and improvement of function and range of motion. However, the addition of joint mobilizations to exercise can accelerate the reduction of short-term pain[53]. The same can be observed in studies included in this SR that combine the use of JM with conventional physiotherapy[36,39,30,43,43,48].

People with chronic pain present reduced functionality, and this loss can be evaluated through functional index instruments[18]. Of the 14 included studies, only seven assessed functionality[36-40,48,49], which shows a deficiency in studies regarding the evaluation of this variable. This is evidenced by the Initiative on Methods, Measurement and Evaluation of Pain in Clinical Trials (IMMPACT) and Outcome Measures in Rheumatology (OMERACT), which bring the importance of assessing both pain and functionality of patients[17].

A systematic review investigated the risks of manual treatment on the vertebral segment and concluded that serious adverse events are rare, the most common are mild, and these are associated with a greater amount of spinal manipulation[57]. Although some studies included in this SR[36,39,43] have investigated adverse events as a secondary outcome and have reported as minimum, there are not enough data to prove this variable due to heterogeneity of the studies.

This review presented some strength points, including the development of the question and the population table, intervention, control/comparison and result (PICO strategy), use of a systematic, explicit and transparent methodology, incorporating internal validity evaluation (risk of bias), independent methodological evaluation by a third reviewer for each of the technical steps involved in the review phases, and a comprehensive survey in most databases, without restrictions. None of the authors reported any conflict of interest.

Nevertheless, there are some limitations in this systematic review that make it impossible to conduct a meta-analysis. Although most of the included studies present low risk of bias, there was a significant heterogeneity regarding the protocol of JM application (different degrees of mobilization, series, repetitions, body segments, type of mobilization – Mulligan, Maitland, Kaltenborn and passive), duration of the chronic condition, treatment performed by more than one professional with different experiences and training times, compared to control groups or placebo using other techniques or treatments that are not related to manual therapy and outcomes assessed in different ways.

From that, future clinical trials should aim to use only the JM technique in experimental groups to standardize the application protocols of the techniques and validate placebo techniques with the use of manual therapy. Based on that, studies can be performed with greater methodological accuracy regarding the application of the technique and can generate greater and more reliable results.

CONCLUSION

According to the results of this review, JM seems to be an effective technique for CMP, when applied alone or in association with other interventions, once it causes pain intensity decrease, improvement on range of motion, strength, functionality, quality of life, with good patient adherence/satisfaction and low adverse events. Based on this review, no specific clinical recommendations can be made on the optimal dose of treatment through JM. Future clinical trials should investigate mobilization types and the dose of treatment according to different musculoskeletal diseases.

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Scalp dysesthesia. Case report

Disestesia do escalpo. Relato de caso

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ABSTRACT

BACKGROUND AND OBJECTIVES: Scalp dysesthesia is characterized by the presence of several localized or diffuse symptoms, such as burning, pain, pruritus or stinging sensations, without objective findings in the physical examination of the patient that can explain and link the existing symptomatology to some other etiology. The aim of this study was to describe a case of scalp dysesthesia, from its clinical and laboratory investigation and the conduct adopted.

CASE REPORT: A 38-year-old male patient, first assigned to the Dermatology Service, with complaints of pruritus in the scalp for 5 years. In the consultation at the Pain Service, the patient complained of daily, intermittent and burning dysesthetic sensations, such as tingling and pruritus in the biparietho occipital region, worsening with heat and associated with severe pain in the cervical region. Upon physical examination, evidence of excoriations associated with this pruritus was found. The patient received conservative pharmacological treatment, with significant improvement of the symptomatology after 3 months.

CONCLUSION: Larger prospective studies are needed to further characterize the pathogenesis of scalp dysesthesia, to generate optimization of the available therapeutic options and consequently improve the care that is given to patients. This report corroborates with some findings already described in the literature, such as the association with cervical alterations and the improvement through the use of low-dose antidepressants and anticonvulsants such as gabapentin.

Keywords: Pain, Paresthesia, Pharmacological treatment.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A disestesia do escalpo caracteriza-se pela presença de diversos sintomas localizados ou difusos, como queimação, dor, prurido ou sensações de picada, sem achados objetivos no exame físico do paciente que possam explicar e ligar os sintomas existentes à alguma outra etiologia. O objetivo deste estudo foi descrever um caso de disestesia de escalpo, desde a sua investigação clínica e laboratorial, até a conduta adotada.

RELATO DO CASO: Paciente do sexo masculino, 38 anos. Primeiramente foi ao serviço de Dermatologia com queixa de prurido em couro cabeludo há cinco anos. Na consulta do Serviço de Dor, o paciente queixava-se de sensações disestésicas como: formigamento e prurido em região biparieto-occipital que piora com o calor, associada à dor de forte intensidade, diária, intermitente e em queimação na região cervical. No exame físico, foram encontradas evidências de escoriações ligadas a esse prurido. O paciente recebeu tratamento farmacológico conservador, com melhora importante do sintoma após 3 meses.

CONCLUSÃO: São necessários maiores estudos prospectivos para caracterizar ainda mais a patogênese da disestesia do escalpo, gerar otimização das opções terapêuticas disponíveis e, consequentemente, melhora na atenção prestada aos pacientes acometidos. Este relato corroborou alguns achados já descritos na literatura, como a associação com alterações cervicais e a melhora por meio do uso de antidepressivos em baixas doses e de anticonvulsivantes como a gabapentina.

Descritores: Dor, Parestesia, Tratamento farmacológico.

INTRODUCTION

Scalp dysesthesia (SD), first described in 1998[1], is classified as one of the several chronic cutaneous pain syndromes. It is characterized by the presence of several localized or diffuse symptoms, such as burning, pain, pruritus or stinging sensations, in the absence of a primary cutaneous disorder[2,3]. It is often underdiagnosed and mistaken for seborrheic dermatitis[4]. It can be caused by a psychiatric condition, nerve injury, muscle tension, or direct surgical injury. It represents a type of chronic pain syndrome with pruritus in the scalp transmitted via afferent amyelinated C fibers[5]. However, there is no consensus on the pathophysiology, in part due to the great anatomical complexity and all components of the scalp region, such as microflora, regionally produced sebum, and neural circuits, which may influence the manifestations of possible alterations in the region[3]. SD's management is not standardized, considering that there are no larger studies[1,2].

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This report aimed to describe a case of SD, from its clinical and laboratory investigation and the conduct adopted.

CASE REPORT

A 38-year-old male patient, first assigned to the hospital's Dermatology Service, with complaints of pruritus in the scalp for five years. Dermoscopic examination discarded seborrheic dermatitis, psoriasis, postherpetic pruritus, and other scalp disorders. The patient was then referred to the Pain Service. During the consultation, the patient complained of pruritus in the scalp, such as tingling and pruritus in the biparietal occipital region, worsening with heat and associated with daily, intermittent and burning severe pain in the cervical region. After a new physical examination, evidence of excoriations associated with this pruritus was found. A magnetic resonance imaging (MRI) of the cervical region and skull was requested, for assessing possible anatomical changes that could explain the picture. The clinical treatment started with gabapentin (300mg) every 12 hours, combined with amitriptyline (12.5mg) in a single daily oral dose.

MNR showed physiological rectification of the cervical spine, peripheral osteophytes with formation of syndesmophytes in the C6 and C7 vertebral bodies, height reduction and dehydration of their respective vertebral discs, characterized by hyposignal on T2, disc-osteophyte complex posterior to C6-C7, with reduced amplitude of the corresponding neuroformations and small central focal protrusion at C3-C4 level.

After the treatment started, an electroneuromyographic study was performed with a sensory threshold test in the parietal, temporal, frontal, and occipital regions, and the bilateral symmetrical sensitivity threshold was within normal limits. Adjusting for daily doses of gabapentin (900mg) and amitriptyline (25mg), the patient presented a significant improvement in pruritus and paresthesia in the occipital region within three months, only showing sporadic episodes associated with the sun exposure in the region related to his work activity.

DISCUSSION

SD is described as one of the several chronic cutaneous pain syndromes, which includes burning mouth, vulvodynia, scrothodinosis, and atypical facial pain[1-3]. It has no preference for race or gender, nor is it considered a serious disease, but it has several negative impacts on the patient's quality of life[6].

It is clinically characterized by the presence of several localized or diffuse symptoms, such as burning, pain, pruritus, or stinging sensations, and more than one dysesthetic sensation may be present in the same area[4]. In order to make the diagnosis, which is essentially clinical, the absence of a primary cutaneous disorder is necessary, and in the literature some dermatoscopic patterns are proposed in patients with this syndrome. In trichoscopy, the most common were trichoptilosis and lesions covered by small and uniform hair, some of which had characteristics of trichorrhexis nodosa, with findings indicating mechanical injury[5]. In the reported case, there were no physical examination findings at the first visit, and only after a new examination, minor excoriations were found.

The patient had cervical spine abnormalities on imaging, which is common, especially in the form of degenerative disc disease. The pathogenesis of this abnormality on cervical imaging may be associated, as stated above, with chronic muscle tension placed on the pericranial muscles and scalp aponeurosis, secondary to spinal disease shown in the image[2,8]. It may or may not be associated with psychiatric disorders, and the most common disorders are persistent depression, generalized anxiety and somatization[2,6]. Although the findings corroborate the etiological theories found in the literature, there is no consensus on the SD origin.

There is no consensus on the SD treatment, but there are some options in the literature demonstrating a good response. As the SD is a syndrome associated with changes of the fine fibers, it is treated as a neuropathy, using gabapentin associated with a low dose of tricyclic antidepressants, in this case, amitriptyline, achieving satisfactory results. Most cases already reported in the literature, as well as the present one, showed good response and even complete absence of reported clinical symptoms[1-4]. Among other forms of treatment, there is the association of drugs, not yet available in Brazil, made of amitriptyline, ketamine and lidocaine[4], in addition to physical exercise and physiotherapy, since the SD can be directly related to cervical and spine problems[8].

This syndrome is characterized as a challenging and frustrating condition for the patient and the physician, as it has no pathogenesis or well-established or even evidence-based treatments. It is necessary to standardize the therapeutic approach by conducting further studies on the subject, such as the best route of administration, dose, and drug.

CONCLUSION

This report corroborates some results already described in the literature, such as the association with cervical alterations and the improvement using low-dose antidepressants and anticonvulsants such as gabapentin.

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About methods and instruments in behavior research

Sobre métodos e instrumentos em pesquisa do comportamento

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Mr. Editor,

Behavioral studies have been developed with reasonable biostatistical reasoning in our field. However, the methodological construction does not always contribute to a better understanding of the pain problem as a behavioral response since it presents biases, mainly because, very often, low-qualified researchers venture into the area. Behavioral research requires correct biostatistical analysis after an appropriate choice of method.

The sciences have become demanding regarding the empirical evidence based on the execution of careful observations and experiments with the purpose of collecting and producing systematic and objective data, and the same occurring in the behavioral sphere – Psychology. The use of research methods must develop according to postulates recommended for its purpose and, therefore, it must be established by standards, including the familiarization of the responsible researcher with the behavioral context intended to research, under the risk of a mistaken result, which in no way contributes to scientific knowledge.

A typical example is the adoption of inventories, whose objective is the study of behavioral variables often used in articles in which authors and reviewers do not always pay attention to the important and fundamental "detail" – the research method.

The Beck Scales, for example, are composed by the Depression Inventory (BDI), Anxiety Inventory (BAI), Hopelessness Scale (BHS) and Suicidal Ideation Scale (BSI) that were designed to measure the intensity of symptoms and are not diagnostic instruments, so they do not ascertain the presence of psychopathological conditions and should be applied to individuals aged 17 to 80 years[1].

In Brazil, it is an instrument for the restricted use of psychologists - mandatory professional registration for its acquisition and application - as it requires specialized technical training. According to the legislation of the Psychological Tests Evaluation System (SATEPSI) of the Federal Council of Psychology (CFP), since April 2018, it is considered as an instrument not adequately validated to Brazilian standards. To date, there is no version to replace it and, therefore, should not be used[2].

It is worth mentioning that the use of behavioral research methods are distinguished from others, because they use methodologies that allow deciphering and decoding the behaviors under certain stimuli, according to their characteristics, as long as the attributes of the studied stimulus and behavior in question are respected. And with that, a researcher wishing to ascertain behavioral conditions must, at least, be qualified to do so.

Confident of contributing to the growth of the subject, I hope to have cleared up some mistakes.

Yours sincerely,

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Pain neuroscience education for patients with musculoskeletal pain

Educação em neurociência da dor para pacientes com dor musculoesquelética

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Dear editor,

The International Association for the Study of Pain (IASP) created the Special Interest Group (2018-2020) on Pain Education. The group aims to "promote pain education to health professionals, patients, communities, & policymakers". Pain neuroscience education (PNE) is one approach of pain education that addresses patient misconceptions regarding the physiology of pain and helps to change their maladaptive beliefs and behavior. PNE is a strategy that incorporates the biopsychosocial model and intends to provide knowledge concerning the neurophysiological, neurobiological, and physical components involving pain experience[1]. Systematic reviews demonstrated the effectiveness of PNE in treating patients with chronic musculoskeletal pain[2,3]. Health professionals can modify the concepts patients have about their pain. Likewise, the beliefs that health professionals have about pain can interfere with patients' beliefs. Recent studies have shown low levels of pain knowledge by health professionals, physical therapy students, and patients. Thus, assessing the knowledge about the neurophysiology of pain is essential to understand and modify thoughts regarding the origin of pain.

Knowledge about pain neuroscience is fundamental to conduct appropriate patient management. A systematic review of the literature showed that strong evidence supports the use of PNE for musculoskeletal disorders[3]. For instance, patients with chronic fatigue syndrome could increase their understanding of the neurophysiology of pain after pain physiology education; Besides, PNE resulted in less worrying in the short term, and long-term improvements in vitality, physical functioning, mental health, and general health perceptions in patients with fibromyalgia. Moreover, patients with lumbar radiculopathy who received a single PNE session before lumbar surgery showed a significant reduction in health care costs three years after lumbar surgery[3]. Despite the available evidence supporting the relevance of health professionals to address the different aspects of the pain experience, they considered a straightforward relationship between pain and harm, which may be related to the lack of specific pain courses in the Brazilian health education programs as Physical Therapy schools[4].

Most of the patients do not understand the mechanisms of pain and, therefore, believe that the pain is always associated with tissue damage. Brazilian patients with musculoskeletal pain also presented a low level of neurophysiological pain knowledge, regardless of the pain predominance based on its mechanism[5]. In conclusion, clinicians should use strategies to improve the level of neurophysiological pain knowledge, which assists the pain management of patients with musculoskeletal pain. Likewise, PNE should be incorporated into the undergraduate curricula of health professionals to enhance the understanding of pain for clinicians and patients.

Sincerely,

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INSTRUCTIONS TO AUTHORS

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WORK PRESENTATION FORMS

Title: The article title must be short, clear, and concise to facilitate its classification. When necessary, a subtitle can be used. It must be sent in Portuguese and English.

Author (s): The full name of the author(s) and affiliations (**in this order: University, College, Hospital, or Department; mini-resumes** are not accepted).

Correspondent Author: Name, current address, zip code, city, state, country and email address. Authors must inform ORCID of all.

Sources of funding (if any).

1. Structured abstract with a maximum of 250 words. For original research articles and clinical trials include **BACKGROUND AND OBJECTIVES, METHODS, RESULTS and CONCLUSION.** For case reports, include **BACKGROUND AND OBJECTIVES, CASE REPORT and CONCLUSION.** For review articles, include **BACKGROUND AND OBJECTIVES, CONTENTS and CONCLUSION**. Include up to six keywords. The use of DeCS - Bireme Health Science Descriptors, available at http://decs.bvs.br/, is recommended.

2. Abstract: The English version of the abstract should be submitted with the article. Include up to six keywords.

3. Body of the Text: Organize the text according to the types of articles described next. In original articles with humans or animals, aspects ethics in addition to the process number and the year of the Ethics Committee or Institution.

For all articles that include patient information or clinical photographs, written and signed consent must be obtained from each patient or family, as well as the Free and Informed Consent Term (FICT) and do not need to forwarded in the submission process. Generic drug names should be used. When trade names are used in the search, these names should be included in parentheses in the chapter "METHODS". Acknowledgments to contributors may be cited at the end of this section, before the references.

ARTICLES TYPES

For all articles that include patient information or clinical photographs, written and signed consent must be obtained from each patient or family member, as well as the Free Informed Consent Form (FICF) and do not need to be submitted in the submission process.

For all articles including information about patients or clinical pictures, the written and signed consent from each patient or relative shall be obtained to be forwarded to the journal with the submission process. Generic drug names shall be used. When trade names are used in the research, these names shall be included in brackets in the chapter "**METHODS**".

1. ORIGINAL ARTICLES

Introduction - This session should briefly describe the scope and evidence-based prior knowledge for research design, based on related bibliographic references. It should clearly include the research objective at the end. Include up to six authors.

Methods - Should include the study design, sample selection processes, ethical aspects, exclusion and inclusion criteria, clear description of interventions and methods used, data analysis as well as the sample power, and applied statistical tests.

Results - These should be objectively described, elucidated by figures and tables when necessary. Include analyses performed and their results.

Discussion - This section should discuss the results found in the research in the light of prior knowledge published in scientific sources, duly cited. It can be divided into subchapters. Include study limitations. Include, whenever possible, the clinical implications of the study and information on their importance and relevance.

Conclusion - This section should present the conclusion of the paper.

Acknowledgments - Acknowledgments to contributors and others may be cited in this section before the references.

References - Must be formatted according to the Vancouver standards (http://www.icmje.org).

Figures and Tables - They should be sent together with the main text of the article in a format that allows editing.

2. CASE REPORT

The BrJP welcomes case reports that are relevant and original. They must be limited to 1,800 words. Include up to three authors. The body structure of the text must contain:

Introduction - This session should briefly describe the scope and evidence-based prior knowledge for the clinical case, based on related bibliographic references.

Case Report - This session should objectively describe the case report with the relevant details.

Discussion - This section should discuss the relevant data of the clinical case in the light of prior knowledge published in scientific sources, duly cited. It should close with the conclusion on the relevant aspects of the case and information on its importance and relevance.

References - Must be formatted according to the Vancouver standards (http://www.icmje.org).

Figures and tables - May be included.

3. REVIEW ARTICLES

Systematic and integrative meta-analyses and reviews from the literature on relevant subjects related to the study and treatment of pain, with systematic and critical analysis of the literature, are welcome.

They should be structured as follows:

Introduction - This session should briefly describe the scope of the review design.

Contents - This session should critically analyze the literature, aiming to survey, gather, critically evaluate the research methodology and gathering the results of several primary studies, seeking to answer a clearly formulated research question using systematic and explicit methods for retrieving, selecting and evaluating the results of relevant studies.

Conclusion - This section should present the conclusion of the review.

Acknowledgments - Acknowledgments to contributors and others may be cited in this section before the references.

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Figures and Tables - They should be sent together with the main text of the article in a format that allows editing.

4. LETTERS

Letters or comments on any article published in the journal be sent, with a maximum of 400 words and up to five references, formatted according to the Vancouver standards (http://www.icmje.org).

REFERENCES

The BrJP adopts the "Vancouver Standards" (http://www.icmje.org) as the style for reference formatting. These should be presented in the text in superscript numerical sequential order. Unpublished papers should not be cited, and preferably, avoid citing abstracts presented at scientific events. References older than five years should only be cited if they are fundamental to the article. Articles already accepted for publication may be cited with the information that they are in the publication process. Up to six authors should be cited and, in case there are more, include et al. after the names. The title of the journal should be abbreviated. Inform the year, volume, issue, and start and end page (matching numbers do not repeat), for example, BrJP. 2019;5(3):251-5.

EXAMPLES OF REFERENCES:

Journal articles

- 1 author - Craig KD. The social communication model of pain. Can Psychol. 2009;50(1):22-32.
- 2 authors - Araujo LC, Romero B. Pain: evaluation of the fifth vital sign. A theoretical reflection. Rev Dor. 2015;16(4):291-6.
- 3 authors - Hampton AJD, Hadjistavropoulos T, Gagnon MM. Contextual influences in decoding pain expressions: effects of patient age, informational priming, and observer characteristics. Pain. 2018;159(11):2363-74.
- More than six authors - Barreto RF, Gomes CZ, Silva RM, AA Signorelli, Oliveira LF, Cavellani CL, et al. Pain and epidemiologic evaluation of patients seen by the first aid unit of a teaching hospital. Rev Dor. 2012;13(3):213-9.

Article with published erratum:

Sousa AM, Cutait MM, Ashmawi HA. Evaluation of the addition of tramadol on the regression time of lidocaine-induced motor blockade. An experimental study in rats evaluating tramadol addition on the regression time of lidocaine-induced motor blockade. An experimental study in rats. Rev Dor. 2013;14(2):130-3. Erratum in: Rev Dor. 2013;14(3):234.

Supplementary Article:

Walker LK. Use of extracorporeal membrane oxygenation for preoperative stabilization of congenital diaphragmatic hernia. Crit Care Med. 1993; 2 (2Suppl1): S379-80.

Book: (when strictly necessary)

Doyle AC, editor. Biological mysteries solved, 2nd ed. London: Science Press; 1991. 477-80p.

Book Chapter:

Riddell RP, Racine NM, Craig KD, Campbell L. Psychological theories and biopsychosocial models in pediatric pain. In: McGrath P, Stevens B, Walker S, Zempsky W. Paediatric Pain. Oxford, 1st Ed. New York: Oxford University Press; 2018. 85-94p.

Theses and dissertations: not accepted.

ILLUSTRATIONS AND TABLES

All illustrations (including figures, tables, and photographs) must be cited in the text, preferably in their entry. List them in Arabic numerals. All should contain title and legend. Use black and white photos and figures and restrict them to a maximum of three. The same result must not be presented in more than one illustration.

Graphic signs used in tables, figures, or acronyms should have their correlation mentioned in the footnote. Figures and tables should be sent in a format that allows editing, according to the following recommendation:

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The submission letter, the manuscript, and the Assignment of Rights (as attachments), the tables must be sent in DOC (Word) format and inserted in the text, at their insertion location. Figures and photos can be sent as attachments. Photos must be scanned with a minimum resolution of 300 DPI, in JPEG format. The file name must express the type and numbering of the illustration (Figure 1, Table 2, for example). Copies or reproductions of other publications will only be allowed upon the express permission of the Publisher or the Author of the original article.

Ethics:

When reporting human studies, authors should indicate whether study procedures are in accordance with ethical standards set by the Human Studies Committee (institutional or national, if applicable) and in accordance with the revised 1975 Helsinki Declaration. in 2000. When dealing with animal studies, authors should indicate whether institutional and / or national guidelines for care and use of laboratory animals were followed. In any clinical or experimental research on humans or animals, this information should be included in the Methods section. The approval number and year of the Research Ethics Committee should be cited.

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The Brazilian Registry of Clinical Trials (ReBEC) is included, which is an open-access virtual platform for the registration of experimental and non-experimental research with humans, in progress or concluded by Brazilian and foreign researchers, which can be accessed at http://www.ensaiosclinicos.gov.br. The study registration number must be included at the end of the abstract.

Use of Abbreviations:

The title and the abstract should not contain abbreviations. Long expressions do not need to be repeated in the text after the INTRODUCTION. After its first mention in the text, preceded by the abbreviation in parentheses, it is recommended to replace it by an abbreviation in capital letters.

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