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EFEITOS AGUDOS DE UMA SESSÃO DE ESTIMULAÇÃO ELÉTRICA NA DOR, AMPLITUDE DE MOVIMENTO E TEMPERATURA EM IDOSOS COM OSTEOARTRITE DO JOELHO: UM ENSAIO CLÍNICO RANDOMIZADO DUPLO-CEGO

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Dissertação apresentada ao Programa de Pós-graduação em Ciências da Reabilitação (PPG-CR) da Universidade de Brasília, como parte dos requisitos necessários à obtenção do título de mestre.

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APRESENTAÇÃO

Em março de 2020 iniciei o mestrado no Programa de Pós-graduação em Ciências da Reabilitação da Universidade de Brasília – Faculdade de Ceilândia, sob orientação do Prof. Dr. João Luiz Quagliotti Durigan. O projeto intitulado "EFEITOS IMEDIATOS DE DIFERENTES MODALIDADES DE ELETROTERAPIA NO CONTROLE DA DOR E TEMPERATURA DE INDIVÍDUOS COM OSTEOARTRITE DE JOELHO" já havia sido aprovado pelo Comitê de Ética e Pesquisa da Universidade Católica de Brasília (CEP/FCE) (CAAE: 85868217.6.0000.8093) em agosto de 2018, e posteriormente registrado na plataforma de ensaios clínicos (https://ensaiosclinicos.gov.br/rg/RBR-74ffv8).

Devido a pandemia causada pelo coronavírus (COVID-19) no Brasil, o governo do Distrito Federal, em 19 de março de 2020, decretou estado de quarentena e isolamento. Foram adotadas pelo governo, diversas medidas de contenção da pandemia, dentre elas o fechamento de Universidades, paralisando por tempo indeterminado todas as atividades presenciais, incluindo a utilização dos laboratórios e outras dependências das instituições de ensino superior no Distrito Federal. Com essa medida e devido ao fato de a população idosa fazer parte do grupo de risco para a contaminação da COVID-19, a continuidade do ensaio clínico ficou comprometida.

Tendo em vista a incerteza acerca do retorno das atividades e as dificuldades de coordenar um ensaio clínico com uma população de risco, em acordo com meu orientador, decidimos pausar o estudo e dar seguimento a realização de uma revisão sistemática com metanálise sobre efeitos da crioterapia no pós-exercício em colaboração com o professor Carlos Pastre da Universidade Estadual Paulista (UNESP). Fomos contemplados no edital FAP publica (Edital 11/2022) para custeio da publicação. A revisão intitulada "DIFFERENT CRYOTHERAPY MODALITIES DEMONSTRATE SIMILAR EFFECTS ON MUSCLE PERFORMANCE, SORENESS AND DAMAGE IN HEALTHY INDIVIDUALS AND ATHLETES: A SYSTEMATIC REVIEW WITH METANALYSIS" foi publicada na revista "Journal of Clinical Medicine", de fator de impacto 3.4. Atualmente fomos contemplados também no edital FAP publica (edital 02/2024) para fomento da publicação do estudo agudo que está submetido na revista "Frontiers in Physiology" de fator de impacto 4.1.

Em Agosto de 2022, o CEP-FCe autorizou a retomada das coletas do estudo inicial do projeto. As coletas foram retomadas em conjunto com um outro projeto que analisou os efeitos de 4 semanas de eletroestimulação em idosos com osteoartrite de joelho, cujo os métodos e resultados também estão apresentados como anexo nessa dissertação.

Nessa dissertação, apresentada como requisito obrigatório para obtenção do título de mestre, serão abordados principalmente os dados referentes aos resultados do estudo que avaliou os efeitos

imediatos da eletroestimulação em idosos com osteoartrite de joelho. Os dados do estudo crônico (métodos e resultados) também estão em anexo, em função das coletas já estarem finalizadas, porém o manuscrito ainda não foi finalizado e está em fase de escrita.

DEDICATÓRIA

Dedico este trabalho à minha família, que incondicionalmente me apoiou, me deu estrutura, amor e apoio, para que pudesse caminhar até aqui. Em especial aos meus pais, Cláudia e José Luiz (in memorian) que em inúmeras vezes abdicaram de seu conforto para que eu tivesse o melhor possível na minha vida.

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Agradeço a minha mãe, Cláudia, por ter feito muito mais do que o possível para que eu tivesse uma educação de qualidade, para que tivesse uma cama para dormir, comida na mesa, afeto, amor e carinho. Não sei se conseguiria retribuir nem em mais duas vidas tudo que fez e faz por mim. Agradeço também por ter herdado do seu sangue a vocação para me comunicar e para ensinar outras pessoas.

Agradeço ao meu pai, José Luiz, que durante 23 anos me permitiu ter sua presença como pai, amigo e meu herói. Os planos de Deus até hoje são incompreensíveis para mim, mas ele quis te chamar para junto Dele antes do que eu imaginasse. Mas o que importa é que hoje eu sigo e cumpro seu legado com muita honra e hombridade, tenho certeza de que estaria celebrando comigo este momento se estivesse aqui, mas tenho mais certeza ainda que está celebrando este momento comigo de onde quer que esteja.

Agradeço aos meus familiares e irmãos por sempre me incentivarem, por sempre me mostrarem o quanto sou amado, acolhido e aplaudido em momentos bons e ruins.

Agradeço aos meus amigos, que estiveram comigo nesta caminhada e estarão em muitas outras pelo apoio, pela amizade, pelos momentos divertidos e boas memórias criadas, vocês sempre estarão no fundo do meu coração. Em especial agradeço ao irmão de outra mãe que a vida me deu, meu amigo, parceiro e sócio Guilherme Monteiro, obrigado por acreditar em mim, por me ouvir e me apoiar.

Agradeço a comunidade de Ceilândia por abraçar o nosso projeto com tanto carinho e por nos confiarem seus corpos para o bem da ciência, agradeço também aos profissionais de saúde que abraçaram e divulgaram nosso projeto. Sem vocês a realização deste projeto não teria sido possível.

Agradeço a Faculdade de Ceilândia por ser a minha segunda casa nos últimos 11 anos, por tudo que pude aprender e viver aqui.

Agradeço ao Professor João e a Professora Rita pelo incondicional apoio na minha orientação, por todas as oportunidades dadas desde a graduação, com vocês aprendi na prática que a educação muda pessoas e pessoas mudam o mundo.

Agradeço a Fundação de Apoio a pesquisa do DF pelo fomento na publicação dos artigos.

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Brasília, 2024

RESUMO

Introdução: A estimulação elétrica (EE) tem sido amplamente utilizada na prática clínica para reduzir a dor e melhorar a função em pacientes com osteoartrite de joelho (OAJ). No entanto, até o momento, nenhum estudo comparou diferentes formas de onda de NMES para alívio da dor a curto prazo relacionado à função da articulação do joelho em pacientes com OAJ.

Objetivo: Avaliar os efeitos a curto prazo das formas de onda de EE sobre a intensidade da dor, a amplitude de movimento (ADM) e a temperatura da pele, administrados como uma intervenção única e unimodal em pessoas com OAJ.

Métodos: Trata-se de um estudo controlado randomizado duplo-cego. Cem participantes, 25 em cada grupo, foram avaliados no início, e 5, 10, 15, 20 e 30 minutos após a sessão de EE. O desfecho primário foi a intensidade da dor medida usando uma escala visual analógica (EVA). Os desfechos secundários incluíram mudanças da linha de base para pós-intervenção na ADM sem dor e na temperatura da pele do joelho. O grupo experimental recebeu três formas de onda de EE: 1) TENS: frequência de pulso de 100 Hz com duração de fase de 200 µs; 2) IFC: frequência de pulso de 100 Hz e frequência portadora de 4000 Hz com duração de fase de 125 µs (10 ms de duração do pulso e 10 ms de intervalo de duty); 3) Aussie: frequência de pulso de 100 Hz e frequência portadora de 4000 Hz (4 ms de duração do pulso e 16 ms de intervalo de duty) com duração de fase de 125 µs. O grupo controle seguiu o mesmo regime, mas com 40 segundos de EE. Os eletrodos foram posicionados ao redor da patela por 20 minutos. As intervenções foram aplicadas uma vez, com acompanhamento a 30 minutos. Todos os participantes de cada grupo concluíram o estudo.

Resultados: A diferença média entre os grupos na mudança na severidade da dor foi de -0,8 cm (Intervalo de Confiança de 95% de -1,6 a 0,1). Esse resultado não atingiu o efeito mínimo significativo de 1,75 cm. Os desfechos secundários mostraram estimativas menos precisas, com intervalos de confiança abrangendo tanto efeitos significativos quanto pequenos.

Conclusão: A EE a curto prazo usando diferentes formas de onda não mostrou superioridade em relação a uma intervenção placebo no alívio da dor, na melhoria da ADM sem dor e na redução da temperatura da pele em pessoas com OAJ. Apesar da EE ser comumente utilizada na prática clínica, nossos achados sugerem que, em comparação com um controle placebo, ela não produz um efeito significativo a curto prazo como tratamento não farmacológico unimodal para indivíduos com OAJ.

Registro: RBR-74ffv8

Palavras-chave: Joelho. Osteoartrite. Estimulação Elétrica. Amplitude de Movimento. Temperatura da superfície da pele.

ABSTRACT

Introduction: Electrical stimulation (ES) has been widely used in clinical practice to reduce pain and improve function in patients with knee osteoarthritis (KOA). However, to date, no studies have compared different NMES waveforms for short-term pain relief related to knee joint function in KOA patients.

Objective: To assess the short-term effects of ES waveforms on pain intensity, range of motion (ROM), and skin temperature, administered as a single and unimodal intervention in people with KOA.

Methods: This is a double-blinded randomized controlled study. One hundred participants, 25 in each group, were assessed at baseline, and 5, 10, 15, 20, and 30 minutes after the ES session. The primary outcome was pain intensity measured using a visual analogue scale (VAS). Secondary outcomes included changes from baseline to post-intervention in pain-free ROM and knee skin temperature. The experimental group received three ES waveforms: 1) TENS: pulse frequency of 100Hz with phase duration of 200 μs; 2) IFC: burst frequency of 100 Hz and carrier frequency of 4000 Hz with 125 μs phase duration (10 ms of burst duration and 10 ms of duty interval); 3) Aussie:

burst frequency of 100 Hz and carrier frequency of 4000 Hz (4 ms of burst duration and 16 ms of duty interval) with 125 μs phase duration. The sham group followed the same regimen but with 40 seconds of ES. Electrodes were positioned over the knee around the patella for 20 minutes. Interventions were applied once, with a follow-up at 30 minutes. All participants from each group completed the trial. Results: The mean between-group difference in change in pain severity was -0.8 cm (95% Confidence interval -1.6 to 0.1). This result did not reach the nominated smallest worthwhile effect of 1.75 cm. Secondary outcomes demonstrated less precise estimates, with confidence intervals spanning both meaningful and small effects. **Conclusion:** Short-term ES using different waveforms did not show superiority over a sham intervention in relieving pain, improving pain-free ROM, and reducing skin temperature in people with KOA. Despite ES being commonly used in clinical practice, our findings suggest that, compared to a sham control, it does not yield a significant short-term effect as a non-pharmacological unimodal treatment for individuals with KOA.

Registration: RBR-74ffv8

Keywords: Knee. Osteoarthritis. Electrical Stimulation. Range of Motion. Skin surface temperature.

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SUMÁRIO

1 Introduction

Knee osteoarthritis (KOA) is a highly prevalent and costly chronic musculoskeletal condition that is commonly linked with pain and disability (Macri et al, 2023; Waheed and Rai 2024). Clinical guidelines typically recommend a combination of non-pharmacological treatments (Macri et al., 2023), including patient education, exercise, and physiotherapy interventions, alongside pharmacological treatments to effectively alleviate pain and symptoms (Macri et al, 2023). Additionally, individuals with KOA may experience joint stiffness, increased joint size, articular crepitation, movement restriction, weakness, and muscle mass loss (Dainese et al, 2022). Exercise therapy is widely recommended as a core treatment to manage pain, enhance quadriceps femoris strength, and improve functional capacity in KOA patients (Mizusaki Imoto et al, 2013).

Complementary treatments include electrical stimulation (ES) modalities, with transcutaneous electrical nerve stimulation (TENS) emerging as the most commonly used in clinical settings, due to its well-established analgesic mechanism, that activates a sophisticated neuronal inhibitory pathway for pain relief (Sluka and Walsh, 2003; Vance et al, 2014; Johnson et al, 2022a). TENS typically utilizes pulsed currents in the frequency range of 1-200 Hz and a pulse width between 100-200 μs, and it has been widely adopted due to its cost-effectiveness in alleviating pain (Almeida et al, 2018). However, the clinical effectiveness of TENS remains controversial, with some studies supporting its use and others refuting its ability to relieve pain in KOA (Sluka and Walsh, 2003; Zeng et al, 2015; Johnson et al, 2022a). Interestingly, Shimoura and colleagues (2019) demonstrated that a single TENS session improved pain inhibition and distance walked in the 6-minute walk test for individuals with KOA (Shimoura et al, 2019). While TENS has been extensively studied for musculoskeletal pain control, limited research exists on the effects of different ES waveforms in clinical practice for controlling pain and providing functional benefits for KOA patients.

Kilohertz frequency alternating currents (KFACs) in the form of the interferential current (IFC) and Russian current are clinically widespread (Ward and Shkuratova, 2002; Ward et al, 2009).

Some theories report that KFAC is perceived to be comfortable and effective for pain control (Ward et al, 2009). IFC generates medium-frequency (4 to 10 KHz) alternating currents, that simultaneously pass through tissues and intersects, creating interference and generating an amplitude-modulated frequency ranging from 1 to 200 Hz (Ward et al, 2009). It has been suggested that IFC reduces skin impedance, thus alleviating the discomfort typically associated with low-frequency currents able to penetrate more deeply into the tissues (Johnson and Tabasam, 2003a). However, this claim requires further investigation (Almeida et al, 2018). Despite the theoretical advantages linked to the medium frequencies of IFC compared to TENS, previous studies indicate that IFC produces similar effects to TENS in managing pain and improving function over time in osteoarthritis (Rutjes et al, 2009).

Another clinically used medium-frequency (1 to 4 KHz) alternating current is the Aussie current, characterized by a burst frequency ranging from 1 to 200 Hz (Ward et al, 2009). It seems that the Aussie current with short-duration bursts (1–4 ms) has a more useful role in rehabilitation than the long-duration bursts of IFC. However, this unique study (Ward et al, 2009) did not evaluate a clinical population in accordance with the Consolidated Standards of Reporting Trials (CONSORT) Statement for Randomized Trials of Non-pharmacological Treatments (Cuschieri, 2019). A systematic review with meta-analysis demonstrated that the limited number of studies and their low quality emphasize the importance of additional clinical trials to compare the efficacy of TENS and IFC in pain management (Almeida et al, 2018). Studies involving KOA patients generally present several consistent methodological constraints, including unconcealed allocation, lack of blinding, inadequate baseline comparability between groups, failure to confirm the grade of KOA in participants, and deviation from the principle of intention-to-treat analysis (Dantas et al, 2019).

Studies with KOA should aim to thoroughly address these methodological criteria in order to ensure robust and comprehensive findings. Additionally, assessing pain and knee range of motion (ROM) is fundamental for evaluating mobility in individuals with KOA (Epskamp et al, 2020). Understanding the complex interaction between inflammation in KOA patients and assessing skin

surface temperature could help clinicians better comprehend the disease's progression and guide targeted interventions, contributing to comprehensive KOA management in clinical settings (De Marziani et al, 2023). The aim of the current study, therefore, was to compare the effects of different short-term ES waveform modalities in people with KOA. Firstly, we hypothesized that ES would relieve pain, improve ROM, and reduce skin temperature, as a surrogate of the inflammation control, compared with a sham intervention. Secondly, we expected no differences amongst TENS, IFC, and Aussie currents in those outcomes.

Methods

Study Design

This study was a randomized, double-blinded placebo-controlled trial carried out in a single visit. The study was performed at the functional performance laboratory of the University of Brasília – Campus Ceilândia and conducted according to the Declaration of Helsinki. Verbal and written explanations of the objectives and methodology of the study were provided to the patients, and those who were willing to participate signed a written informed consent form approved by the local ethics committee (CAAE 62256516.2.0000.0030). The study was registered in the Brazilian Registry of clinical trials (https://ensaiosclinicos.gov.br) (RBR-74ffv8) (Cuschieri. 2019).

A baseline assessment was performed, followed by assessments at 5, 10, 15, and 20 minutes during the treatment, and a final assessment conducted 30 minutes after the end of the treatment. Each participant was assessed at the same time of day in the laboratory. The same evaluator (KP) performed all the assessments at all moments of data collection. Another researcher (MB) was responsible for modulating the physical parameters of ES, without knowledge of the evaluator or therapist. A third researcher (LH), acting as the therapist, applied ES electrodes to the specified location, initiated the therapy, and managed the intensity, with incremental increases every 5 minutes, based on the participant's maximal perception of tolerable discomfort. Prior to the commencement of data collection, all researchers underwent training, encompassing both scientific information and clinical instruction pertaining to ES for KOA. Adherence was defined as completing a full intervention session for all

participants included in the study. At the end of each session, the assessor who conducted the data collection assessments checked for the occurrence of adverse effects.

Participants were allocated into four groups of 25 participants each; three experimental groups, that received TENS, AUSSIE, or IFC, and a sham group that received a sham intervention. Allocation was performed by blocked randomization. A list was generated on www.random.org with an aleatory sequence with group names and the sample was allocated in the order that they were recruited. Just before the intervention started, the random allocation of each participant was disclosed (McAlindon et al, 2015).

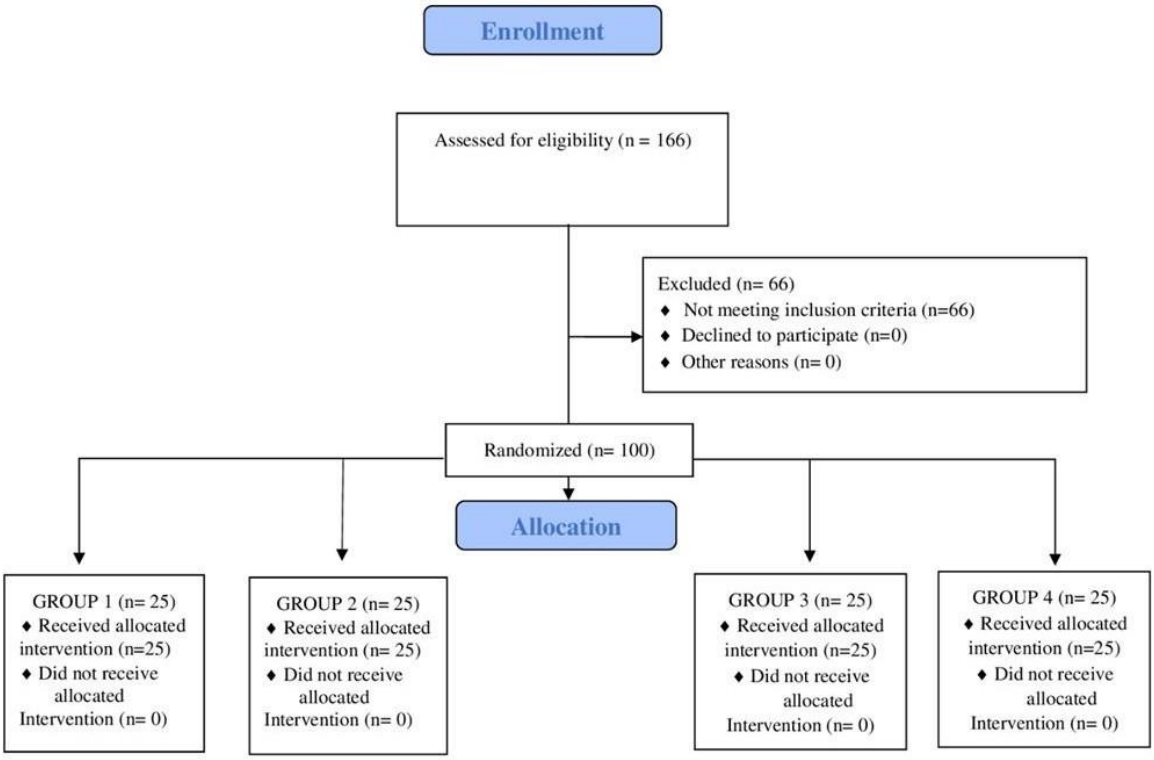

Figure 1: CONSORT flowchart

Blinding

The researcher who applied the ES and the participants were blinded to treatment allocation. To this end, another researcher performed the programming of each ES tested and placed a black cover on the ES device panel to maintain the parameters blinded for the researcher and the participants, except for the current intensity.

Participants

Participants were recruited through local clinics and hospitals, via advertising flyers. To be eligible for participation, patients were required to show both symptomatic and radiographic indications, as per the Kellgren-Lawrence scale, with a minimum grade of 2 (indicating at least mild radiographic osteoarthritis), observed in at least one knee compartment (Kellgren and Lawrence, 1957). Participants were required to meet the following criteria: aged 60 years or older; engage in a minimum of 45 minutes per week of accumulated physical activity at a moderate intensity level; and report a pain intensity equal to or exceeding 4 cm on a 10-cm visual analogue scale. The exclusion criteria were: individuals who had undergone physiotherapy in the previous 3 months, received knee injections in the previous 6 months, had medical constraints, such as cardiorespiratory, neurological, or rheumatological dysfunctions, had undergone prior hip, knee, or ankle surgery, and those with chronic conditions leading to knee pain.

Intervention

ES groups

Participants were randomized into three experimental groups: 1) TENS: pulse frequency of 100 Hz with 200 µs phase duration; 2) IFC: burst frequency of 100 Hz and carrier frequency of 4000 Hz (10 ms of burst duration and 10 ms of duty interval) with 125 µs phase duration; and 3) Aussie: burst frequency of 100 Hz and carrier frequency of 4000 Hz (4 ms of burst duration and 16 ms of duty interval) with 125 µs phase duration (Table 1). NMES was administered during a single session exclusively to the more affected knee, within a precisely controlled air-conditioned environment set at 21°C (±2). Electrodes were positioned at four points around the patella with the participant in dorsal decubitus, with their legs extended and relaxed. Four self-adhesive electrodes, each 25 cm², were placed around the patella, and 2 channels of the ES equipment were used. The electrodes were placed next to the medial condyle of the femur and head of the fibula for channel 1 and the lateral condyle of the femur and next to the medial region of the tibial plateau, with the main aim of providing pain relief rather than provoking muscle contraction (Shimoura et al, 2019). When the therapy started, the patient was asked to provide feedback on the sensory perception of the ES application and to allow for an increase in intensity until reaching maximum tolerated discomfort at the sensory threshold. After starting the ES

application, the intensity was gradually raised every 5 minutes to achieve a similar level of sensory threshold as at the start of treatment. Each intervention group received a 20-minute session.

Table 1: Physical parameters of ES and SHAM groups

PARAMETERS	TENS	IFC	Aussie	Sham
Pulse frequency (Hz)	100	100	4000	100
Pulse width (μs)	200	125	125	NA
Carrier frequency (Hz)	-	4000	4000	NA
Burst frequency (Hz)	-	100	100	NA
Inter-burst interval (ms)	-	10	4	NA
Therapy duration (min)	20	20	20	20;

Hz: Hertz; μs: microseconds; ms: milliseconds; min: minutes; NA: not applicable.

Sham group

Participants received a current with a pulse frequency of 100 Hz with an intervention duration of 19 minutes and 20 seconds, and 40 seconds of sham intervention, as previously described (Zeng et al., 2015).

Outcome measures

All outcomes were measured by the same blinded assessor before and after the intervention. For painless range of motion, assessments were conducted pre-intervention, immediately after the end of the intervention,

and 30 minutes after the end of the intervention. Pain and temperature data were collected at 5, 10, 15, and 20 minutes during the intervention, as well as 30 minutes after the end of the intervention. The main outcome measures included pain measured on the visual analogue scale (VAS), with a minimum clinically important difference of 1.75 cm based on previous published data (Dantas et al, 2019), as well as knee superficial temperature, pain intensity, and knee range of motion (with and without pain).

Primary outcome

The primary outcome was pain intensity assessed using the VAS. This self-reported pain score is a valid and reliable measure among people with KOA (Hawker et al, 2011). A ten-centimeter graded scale was presented to the participant, who was asked to rate their pain, with 0 representing no pain and 10 representing the worst pain. Pain intensity was measured before the intervention, at 5, 10, 15, and 20 minutes during the treatment, and during a follow-up assessment 30 minutes after the end of the treatment.

Secondary outcomes

Superficial knee temperature

Superficial knee temperature was measured as a surrogate for knee surface inflammation (Denoble et al, 2010; De Marziani et al, 2023). Three images were captured of the lateral, medial, and frontal regions of the knee, and the average temperature on these three images was used. Superficial knee temperature was measured at 5, 10, 15, and 20 minutes of treatment, as well as a follow-up of 30 minutes after the end of treatment. A real-time thermal imager with a built-in 640 x 480-pixel resolution was employed, able to measure temperatures spanning from -20°C to +1200°C. The device boasted a sensitivity of 0.08ºC and an accuracy within ±2ºC for absolute temperature measurements (Flir C2™, Wilsonville, Oregon, USA). Thermal analysis centered on the mean temperature derived from three knee images, each captured using specific software (FLIR Thermal Studio Suite™, Wilsonville, Oregon, USA). The reliability for mean temperature measurement demonstrated excellent intra-rater reliability (intraclass correlation coefficient [95% confidence interval (CI)] = 0.91 [0.87– 0.93]). The intraclass correlation coefficient was calculated by the authors, comparing measures taken before the

data collection. Continuous data collection occurred at five-minute intervals during treatment and 30 minutes post-treatment to ensure the physiological effects of ES. A reduction of 0.5°C in the knee temperature was considered to be the minimum clinically important difference for KOA studies, according to previously published data (Denoble et al, 2010).

Pain-free range of motion

For assessment of the pain-free ROM, a trained examiner, following prior training, positioned the goniometer aligned with the lateral condyle of the femur and instructed participants to extend the knee until reaching their tolerable pain threshold (Epskamp et al, 2020).

Statistical analyses and sample size

The quantitative variables to characterize the sample are respectively expressed as mean and standard deviation (SD) or frequency distribution. The Levene test detected normal distribution for the majority of variables. Accordingly, parametric statistics were principally performed. All outcomes (primary and secondary) were assessed by two-way ANOVA with "time" (six levels: pre, 5, 10, 15,20 minutes, and 30 minutes post intervention for pain and temperature. Three levels: pre, 20 minutes, and 30 minutes after the end of intervention) and "groups" (four levels: TENS, IFC, Aussie, and Sham) as factors. Post hoc analyses (Bonferroni test) were performed when appropriate. Effect sizes were determined using partial eta squared ($\eta\rho 2$) for ANOVA. The Cohen's d was used for the effect sizes and provided benchmarks to define small ($\eta\rho 2 = 0.01$), medium ($\eta\rho 2 = 0.06$), and large ($\eta\rho 2 = 0.14$) effects (Lakens. 2013).

SPSS statistical software™ was used (version 20; IBM Corp., Armonk, USA). For all tests, the significance level was set at $p < 0.05$. Missing data for outcome measures were imputed using the expectation-maximization method (da Silva Almeida et al, 2022). The sample size was calculated based on the mean score on the VAS for pain, reported previously for a similar population of KOA patients (8.10 ± 1.23 cm) (Shimoura et al, 2019). An assumption was made that a clinically significant change in VAS scores would have to

correspond to 30% of the total value, and a significance level of 0.01 and 95% power were adopted. These criteria led to an estimated minimum sample size of 25 in each group (Shimoura et al, 2019).

Results

Initially, between March 2019 and August 2023, 166 participants were recruited through public health units, social networks, and banners, of which one hundred eligible men and women with KOA were included and randomized for the study. Of the 66 excluded individuals, 42 individuals received corticosteroid injections during the three months before treatment, 13 individuals were receiving another physical therapy intervention, eight individuals reported knee surgery, and three individuals were excluded due to other neuromuscular conditions. The recruitment process is described in the CONSORT diagram (Figure 1). In March 2020, the trial was halted due to the COVID-19 pandemic, since the sample was in a high-risk group. Data collection recommenced in August 2022 following progress with vaccinations and concluded in August 2023.

Table *2*: Baseline characteristics of participants.

	TENS	**IFC**	**AUSSIE**	**SHAM**
	mean (SD)	**mean (SD)**	**mean (SD)**	**mean (SD)**
Age *(yr)*	67.76 (4.78)	67.60 (3.64)	69.00 (5,21)	68.08 (5.28)
Weight (*kg)*	70.34 (7.61)	69.07 (7.61)	71.26 (8.84)	72.66 (6.91)
Height (*m*)	1.57 (0.65)	1.58 (0.68)	1.59 (0.61)	1.59 (0.54)
BMI (kg/m^2)	28.53 (2.88)	27.67 (3.37)	28.54 (3.29)	28.73 (3.19)

Data are reported as mean (standard deviation). BMI: body index mass.

Adherence and adverse events

All the included participants received the intervention and there were no drop-outs. Since the study protocol entailed a single session during one visit to the research laboratory, researchers assessed and offered treatment to all eligible individuals. No adverse effects were observed.

Primary outcome

A significant interaction was observed between time and groups ($p = 0.001$; Figure 2A), and a significant main effect of time ($p < 0.001$). At baseline, no significant differences were observed between groups ($p > 0.05$).

The TENS group (mean [95% CI]: baseline =7.88 [7.29 – 8.47]; 5 minutes of treatment =1.64 [0.73 – 2.54]; 10 minutes of treatment =1.60 [0.86 – 2.33]; 15 minutes of treatment =1.56 [0.75 – 2.36]; 20 minutes of treatment =1.76 [0.90 – 2.61]; 30 minutes after the end of intervention =1.40 [0.79 – 2.00]) presented significant decreases in pain in all the comparisons between the time-points. Considering the comparison between baseline and 20 minutes of treatment, a significant pain decrease of -6.12 [4.47; 7.76] ($p <0.001$) was observed. A significant decrease was also observed between baseline and thirty minutes after the end of treatment, -6.48 [5.11; 7.84] ($p <0.001$). Table 3 presents the effect size data for the primary outcome.

The IFC group (baseline =7.88 [7.29 – 8.47]; 5 minutes of treatment =3.16 [2.25 – 4.06]; 10 minutes of treatment =1.56 [0.82 – 2.29]; 15 minutes of treatment =1.56 [0.82– 2.29]; 20 minutes of treatment =0.68 [-0.17 – 1.53]; and 30 minutes after the end of intervention =0.21 [-0.39 – 0.81]) presented a significant decrease in pain in all the comparisons between the time-points. Considering the comparison between baseline and 20 minutes of treatment, a significant pain decrease of -7.20 (5.55 – 8.83) ($p <0.001$) was observed. A significant decrease was also observed at thirty minutes after the end of treatment -7.66 (6.31 – 9.02) ($p <0.001$).

The Aussie group (baseline =7.76 [7.17 – 8.35]; 5 minutes of treatment =3.16 [2.25 – 4.06]; 10 minutes of treatment =2.15 [1.14 – 2.88]; 15 minutes of treatment =0.56 [-0.24 – 1.36]; 20 minutes of treatment =0.92 [0.06 – 1.77]; and 30 minutes after the end of intervention =0.34 [-0.26 – 0.94] presented significant decreases in pain in all the comparisons between the time-points. Considering the comparison between baseline and 20 minutes of treatment, a significant pain decrease of -6.84 (5.20 – 8.47) ($p <0.001$) was observed. A significant decrease was also observed at thirty minutes after the end of treatment, -7.41 (6.06 – 8.77) ($p <0.001$).

The SHAM group (baseline =7.54 [6.95 – 8.13]; 5 minutes of treatment =3.35 [2.44 – 4.25]; 10 minutes of treatment =1.65 [0.92 – 2.39]; 15 minutes of treatment =0.71 [-0.08 – 1.51]; 20 minutes of treatment =1.13 [0.28 – 1.98]; and 30 minutes after the end of intervention =0.33 [-0.27 – 0.93]) presented significant decreases in pain in all the comparisons between the time-points. Considering the comparison between baseline and 20

minutes of treatment, a significant pain decrease of -6.40 (4.77 – 8.03) (p <0.001) was observed. A significant decrease was also observed at thirty minutes after the end of treatment, -7.20 (5.85 – 8.56) (p <0.001).

In addition, at thirty minutes after the end of treatment, a difference was found between TENS and IFC (p value; mean difference [95% CI]: p= 0.042; 1.18 [0.27 – 2.35).

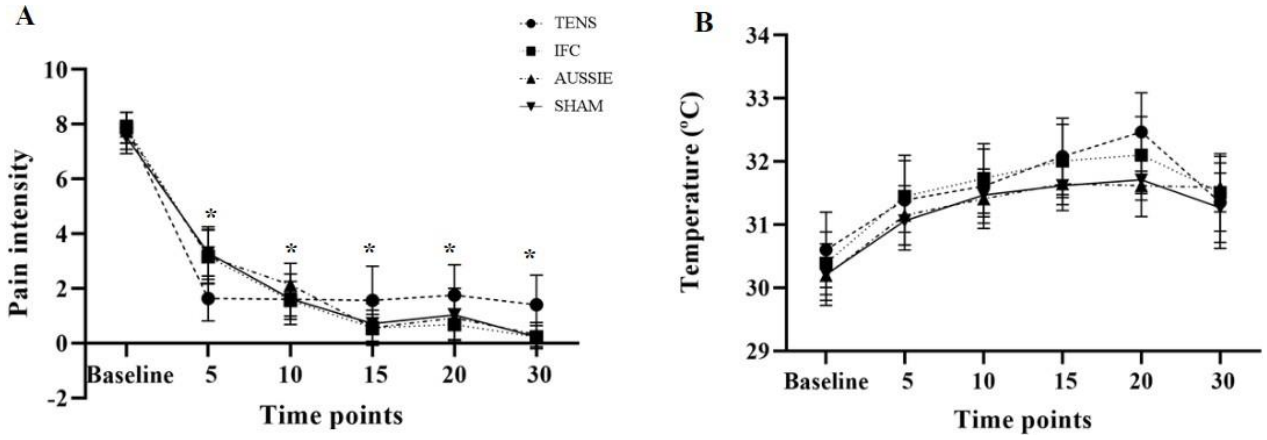

Figure 2. Pain intensity and skin surface temperature comparisons. A: Mean and 95% confidence interval for pain intensity measured by the visual analogue scale pre-intervention, after 5, 10, 15, and 20 minutes of intervention, and 30 minutes after the end of the intervention. B: Mean and 95% confidence interval for skin surface temperature pre-intervention, after 5, 10, 15, and 20 minutes of intervention, and 30 minutes after the end of the intervention. * Main effect of time (P<0,05)

Table 3. Between group effect sizes for pain intensity

OUTCOME		Effect size, *d (95%CI)*					
		TENS vs IFC	**TENS vs AUSSIE**	**TENS vs SHAM**	**IFC vs AUSSIE**	**IFC vs SHAM**	**AUSSIE vs SHAM**
VAS	5’	-0.73(0.16;1.30)	-0.73(-1.30;-0.16)	-0.82(-1.40; -0.24)	-0.01 (-0.55; 0.5)	-0.090(-.500.65; 0.46)	-0.09 (-0.65; 0.46)
	10’	-0.02 (-0.57; 0.54)	-0.26 (-0.82; 0.29)	-0.02 (-0.57; 0.52)	-0.28(-0.84; 0.27)	-0.04 (-0.59;0.50)	0.24 (-0.32;0.80)
	15’	0.48 (-0.08; 1.04)	-0.48 (-1.04;0.08)	0.41 (-0.15; 0.97)	0.00(-0.55; 0.55)	-0.07 (-0.63; 0.48)	-0.07(-0.63; 0.48)
	20’	0.52 (-0.04; 1.08)	-0.40(-0.96;0.16)	0.30 (-0.25;0.86)	-0.12(-0.67; 0.44)	-0.22 (-0.77; 0.34)	-0.10 (-0.66; 0.45)
	30’	0.57 (-0.01; 1.14)	-0.51 (-1.07; 0.05)	0.51 (-0.05; 1.08)	-0.06(-0.62; 0.49)	-0.06 (-0.61; 0.50)	0.00 (-0.55; 0.55)

Effect sizes (*d*): trivial (<0.20); small (0.20-0.49); moderate (0.50-0.79); large (0.80-1.29); very large (>1.30).

Effect sizes (*f*): small (0.10-0.24); medium ((0.25-0.39); large (≥0.40).

Secondary outcomes

There were no significant interactions between time and groups for pain-free ROM ($p = 0.47$) and skin temperature ($p = 0.20$). However, a significant main effect was observed for both outcomes ($p < 0.001$). Regarding the ROM, there was a significant increase of 4.44 ($p < 0.001$; 1.84 – 7.05) in the comparison of baseline versus 20 minutes of treatment, of 6.39 ($p < 0.001$; 03.57 – 9.21) in the comparison of baseline versus thirty minutes after the end of treatment, and of 1.94 ($p = 0.042$; 0.50 – 3.83) in the comparison of 20 minutes of treatment versus thirty minutes after the end of treatment.

Regarding skin temperature (baseline =30.21 [29.97 – 30.45]; 5 minutes of treatment =31.26 [30.99 – 31.53]; 10 minutes of treatment =31.55 [31.31 – 31.79]; 15 minutes of treatment =31.84 [31.60 – 32.07]; 20 minutes of treatment =31.97 [31.72 – 32.22]; 30 minutes after the end of intervention =31.42 [31.14 – 31.71]), significant increases were observed in all the comparisons between the time-points. The comparison between baseline and 20 minutes of treatment showed a significant pain decrease of -1.75 (-2.28 – 1.23) ($p < 0.001$). A significant decrease was also observed at thirty minutes after the end of treatment -1.21 (-1.75 – -0.67) ($p < 0.001$).

Discussion

The findings of the current study raise important considerations regarding the short-term efficacy of a single administration of different waveforms of ES compared to a sham for pain management in knee KOA patients. The results demonstrate that all three intervention groups, as well as the sham, exhibited similar effects in decreasing pain intensity as measured by VAS scores. Furthermore, no significant effects of ES and sham were observed on the secondary outcomes, of pain-free ROM and skin surface temperature. These results suggest that the placebo (represented by the sham group) effect may play a significant acute role in pain management outcomes across the various intervention groups (Colloca and Grillon, 2014; Colloca, 2019). Our findings can assist clinical physiologists to understand the impact of short-term ES on pain management in KOA patients, thereby allowing for the development of more rational stimulation strategies.

It is well-known that TENS is effective for nociceptive and nociplastic pain mechanisms based on reducing both peripheral and central sensitization (Melzack and Wall, 1965) and activation of endogenous opioids (Sluka and Walsh, 2003; Vance et al, 2022), and it may improve exercise tolerance in individuals who experience pain. However, the physiological effects of IFC are not well-established (Noble et al., 2000; Almeida et al., 2018). It is claimed that IFC decreases the stimulation of cutaneous sensory nerves near the electrodes while increasing its effect on deep tissues. Several theories have been proposed to explain its analgesic effect, including the gate control theory, descending pain suppression pathway, and physiological blockade (Noble et al, 2000). Another theory to consider is that KFACs, such as IFC and the Aussie current, may be more effective in reducing skin impedance and increasing tissue penetration, thus potentially providing greater patient comfort (Pantaleão et al, 2011; Bae and Lee, 2014). This could potentially be associated with higher effectiveness in pain relief. Currently, there is a lack of extensive experimental research exploring the mechanism of action of IFC or the Aussie current

for pain management. Claims regarding these modalities are often based on the mechanism of action observed with TENS. Therefore, further studies are needed to investigate the analgesic mechanism of IFC and the Aussie current in KOA patients.

The current study suggests that the positive impact of ES on pain is minimal and may not be deemed significant. The comparable outcomes across the three intervention groups and the placebo group suggest that non-specific factors, such as placebo effects, may also significantly contribute to pain reduction. Our findings underscore the importance of patient perception and psychological factors in pain management. The placebo effect is known to be influenced by factors such as treatment expectations, patient-provider interactions, and contextual cues (Colloca and Grillon, 2014). The fact that all three intervention groups showed similar results to the sham group suggests that these psychosocial aspects of treatment may have a substantial impact on pain outcomes (Colloca and Grillon, 2014; Blythe et al, 2019; Colloca, 2019). Due to the multidimensional nature of pain, individuals exhibit a "neural signature", generated by a neural network distributed throughout the brain(Moseley, 2003). The theory of the neuromatrix of pain (Melzack and Wall, 1965), emphasizes that an individual's beliefs and cognition can determine whether they will experience pain (Kovacs et al, 2011).

Our results regarding the mean difference (~-6.84) clearly demonstrate that all experimental conditions of ES and placebo reached the minimum detectable change for knee pain, described as -1.99 according to (Tubach, 2005). This improvement can be explained by the neuromatrix theory of pain, as well as other factors that can influence post-consultation pain improvement (Dieppe et al, 2016; Skou and Roos, 2019). Contextual factors present in healthcare treatment can impact outcomes by generating expectations, memories, and feelings. Essentially, a patient exposed to a positive context may experience a placebo effect (Rossettini et al, 2018), which can play a relevant role in the treatment and should not be ignored. Studies show that placebos can improve subjective and objective indicators of pain by up to 30 to 40% (Hróbjartsson and Gøtzsche, 2001; Wager and Atlas, 2015; Vase et al., 2015). The perception of being monitored or having behavior judged creates beliefs about the researcher's expectations, known

as the Hawthorne effect, which can also directly influence the results (McCambridge et al., 2014). In addition, it has been demonstrated that patients with higher initial pain levels are more likely to have an elevated response to the placebo (Ferreira et al, 2013; Vase et al, 2015), which could also explain our results. Future research should aim to elucidate the underlying acute mechanisms of both ES and placebo effects, in order to better inform clinical decision-making and optimize treatment approaches in KOA patients.

Some studies have shown that, to reduce the persistence of pain at higher intensities by addressing central or peripheral sensitization, a period for recovery and positive reorganization of neuroplasticity induced by long-term treatment is necessary (Noble et al, 2000; Johnson and Tabasam, 2003b; Bae and Lee, 2014). For example, in studies involving fibromyalgia patients, mechanical hypersensitivity decreased not only at the site of TENS (spine) but also outside the treatment site (leg) when compared to placebo or no TENS. This reduction suggests a clinical improvement in both peripheral and central sensitization. Repeated administration of active TENS over one month led to improvements in movement-evoked pain and other clinical outcomes among women with fibromyalgia who were on a stable medication regimen (Dailey et al, 2013). Similarly, a clinical trial involving patients with KOA pain, demonstrated that both high and low frequency TENS decreased mechanical hypersensitivity at the knee (Iijima et al, 2020). Consequently, it is plausible to suggest that a single treatment administration, as in the present study, would not completely inhibit the chronic sensation of pain.

Regarding the secondary outcomes, the observed between-group differences were smaller than the smallest meaningful effects, showing unclear clinical importance for KOA patients. Recent comprehensive analyses have highlighted a connection between the temperature of the skin surface over joints and the presence and severity of inflammatory and degenerative joint conditions, such as rheumatoid arthritis and osteoarthritis (Varju, 2004; Schiavon et al, 2021). In our study, an overall increment in skin temperature was observed during both ES treatment and Sham. These results can be partially explained by the challenges that older patients face in temperature control, since they tend to have difficulty maintaining temperature, and cooler knee

temperatures may be linked to the natural decline in body temperature associated with aging (Ferreira et al, 2008). The estimates of the effect of the present protocol did not provide clear implications regarding whether ES plays a critical role in increasing pain-free ROM. However, these preliminary data could support future randomized controlled trials. Thus, further research into the effect of ES on secondary outcomes is feasible, but significant effects appear unlikely, as our results clearly indicate a similar pain reduction compared to the Sham group.

It is important to acknowledge certain limitations of this study. We tested only a single administration of ES and did not plan to perform a follow-up of the primary outcomes, as recommended by the CONSORT guidelines (Cuschieri, 2019). In addition, we conducted ES at the sensory threshold level, positioning the electrodes over the knee, in an attempt to avoid paradoxical contractions (Shimoura et al, 2019). However, this approach may have introduced a limitation to the study, as stimulation intensity is crucial for achieving effective pain relief; higher intensity is typically associated with better analgesic effects (Vance et al, 2022). Therefore, this factor could have contributed to the significant effect size observed in the sham group compared to the treatment groups. Future clinical trials should investigate the effects of repeated daily delivery of TENS, Aussie current, and IFC—similar to the ES used clinically—on pain, fatigue, function, and quality of life in individuals with KOA.

Conclusion

Short-term ES of different waveforms did not show superiority over a sham intervention in relieving pain, improving pain-free ROM, or reducing skin temperature in people with KOA. Despite ES being commonly used in clinical practice, our findings suggest that it does not yield a significant short-term effect compared to a sham control as a non-pharmacological treatment for individuals with KOA.

2 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

3 Author Contributions

Concept/idea/research design: K. Porto Azevedo. C. Cadena Almeida. P. Azevedo Garcia. J.L. Quagliotti Durigan

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Data analysis: K. Porto Azevedo. C. Cadena Almeida. P. Azevedo Garcia. J.L. Quagliotti Durigan

Project management: K. Porto Azevedo. C. Cadena Almeida. P. Azevedo Garcia. J.L. Quagliotti Durigan

Fund procurement: K. Porto Azevedo. C. Cadena Almeida. J.L. Quagliotti Durigan

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Providing facilities/equipment: P. Azevedo Garcia. J.L. Quagliotti Durigan

Providing institutional liaisons: P. Azevedo Garcia. J.L. Quagliotti Durigan

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Consultation (including review of manuscript before submitting):

I K. Porto Azevedo. C. Cadena Almeida. P. Azevedo Garcia. J.L. Quagliotti Durigan

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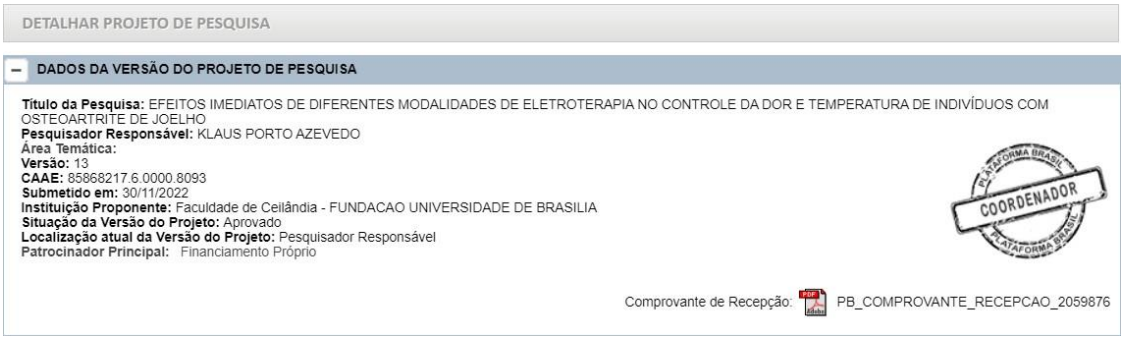
ANEXOS

ANEXO I- Aprovação do Comitê de Ética e Pesquisa



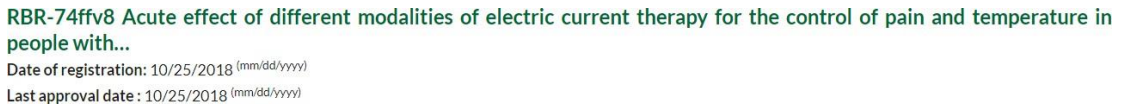
DETALHAR PROJETO DE PESQUISA

DADOS DA VERSÃO DO PROJETO DE PESQUISA

Título da Pesquisa: EFEITOS IMEDIATOS DE DIFERENTES MODALIDADES DE ELETROTERAPIA NO CONTROLE DA DOR E TEMPERATURA DE INDIVÍDUOS COM OSTEOARTRITE DE JOELHO
Pesquisador Responsável: KLAUS PORTO AZEVEDO
Área Temática:
Versão: 13
CAAE: 85868217.6.0000.8093
Submetido em: 30/11/2022
Instituição Proponente: Faculdade de Ceilândia - FUNDACAO UNIVERSIDADE DE BRASILIA
Situação da Versão do Projeto: Aprovado
Localização atual da Versão do Projeto: Pesquisador Responsável
Patrocinador Principal: Financiamento Próprio

Comprovante de Recepção: PB_COMPROVANTE_RECEPCAO_2059876

ANEXO II – Registro do estudo na plataforma REBEC



RBR-74ffv8 Acute effect of different modalities of electric current therapy for the control of pain and temperature in people with...
Date of registration: 10/25/2018 (mm/dd/yyyy)
Last approval date : 10/25/2018 (mm/dd/yyyy)

ANEXO III – Comprovante de submissão do manuscrito "*SHORT-TERM EFFECTS OF SINGLE ADMINISTRATION OF ELECTRICAL STIMULATION WAVEFORMS ON PAIN, RANGE OF MOTION AND SKIN TEMPERATURE IN KNEE OSTEOARTHRITIS: A DOUBLE-BLINDED CLINICAL TRIAL".* Na revista frontiers in Physiology.

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para mim

Traduza para o português

Dear Dr Azevedo

We are pleased to inform you that we have received the manuscript "SHORT-TERM EFFECTS OF SINGLE ADMINISTRATION OF ELECTRICAL STIMULATION WAVEFORMS ON PAIN, RANGE OF MOTION AND SKIN TEMPERATURE IN KNEE OSTEOARTHRITIS: A DOUBLE-BLINDED CLINICAL TRIAL" to be considered for publication in Frontiers in Physiology, section Skeletal Physiology.

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Best regards,
Your Frontiers in Physiology Team,

APÊNDICE

APÊNDICE I – Certificados dos resumos apresentados em congresso

CERTIFICADO

Certificamos que o trabalho **CRIOTERAPIA DE CORPO PARCIAL E CORPO INTEIRO TÊM EFEITOS SEMELHANTES NA DOR PERCEBIDA, DESEMPENHO MUSCULAR E DANO MUSCULAR EM INDIVÍDUOS SAUDÁVEIS E ATLETAS: UMA REVISÃO SISTEMÁTICA COM META ANÁLISE** de autoria de **Klaus Porto Azevedo, Júlia Aguillar Ivo Bastos, Ivo Vieira de Sousa Neto, Carlos Marcelo Pastre e Joao Luiz Quagliotti Durigan** foi apresentado na modalidade e-pôster durante o **I Simpósio Interdisciplinar em Ciências da Reabilitação (SIMReab)**, realizado pelo Programa de Pós Graduação em Ciências da Reabilitação da Universidade de Brasília (PPGCR-UnB), no dia 20 de novembro de 2021.

ALINE MARTINS DE TOLEDO
Coordenadora do PPGCR

MARIA AUGUSTA DE A. MOTA
Presidente do SIMREAB

ORGANIZAÇÃO PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA REABILITAÇÃO REALIZAÇÃO Grupo ACOLHER & CUIDAR APOIO

EFEITOS DA ELETROESTIMULAÇÃO EM INDIVÍDUOS COM OSTEOARTRITE DE JOELHO

CERTIFICADO DE EXTENSÃO

Universidade de Brasília
Decanato de Extensão
Secretaria de Administração Acadêmica

Certificamos que, KLAUS PORTO AZEVEDO, CPF 056.073.301-17, participou da atividade APRESENTAÇÃO DE TRABALHOS, com carga horária de 2 hora(s) e que pertence a Atividade de Extensão VI CTS , promovido pelo(a) FACULDADE DE CEILÂNDIA, na função de PARTICIPANTE, com frequência 100%. Com a seguinte observação: "EFEITOS DA ELETROESTIMULAÇÃO EM INDIVÍDUOS COM OSTEOARTRITE DE JOELHO" - K.P.Azevedo; C.C.Almeida; P.A.Garcia; J.L.Q.Durigan. A atividade foi realizada no período de 26 de Setembro de 2023 a 26 de Setembro de 2023.

Brasília, 18 de Outubro de 2023

OLGAMIR AMANCIA FERREIRA
Decana de Extensão

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Apêndice II – Métodos e Resultados do estudo crônico

EFFECTS OF DIFFERENT ELECTRICAL STIMULATION WAVEFORMS COMPARED TO SHAM ELECTRICAL STIMULATION ON PAIN, FUNCTION AND SKIN TEMPERATURE IN KNEE OSTEOARTHRITIS: A DOUBLE-BLINDED CLINICAL TRIAL

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Methods

Study Design

This study was a randomized, double-blinded placebo-controlled trial carried out in a single visit (figure 1). The study is reported according to the Consolidated Standards of Reporting Trials (CONSORT) Statement for Randomized Trials of Nonpharmacologic Treatments. (Cuschieri, 2019).

A baseline assessment was performed on the first moment and no differences were found between groups, before the treatment or sham intervention. After this, the assessment was performed after 12 session of treatment (3 session per week),. Each patient was assessed in the same period of the day in a physiotherapy research laboratory by the same assessor (KP).

To avoid bias, this study was double-blinded. One person (KP) made all assessments, while another researcher (MB) modulated the physical parameters of ES without knowing the assessor or the therapist. The therapist (LH, JG, DN, IA) applied the ES electrodes, initiated therapy, and adjusted the intensity every 5 minutes based on participant tolerance. All researchers received training on the scientific and clinical aspects of ES related to KOA before data collection began.

Participants were allocated into four groups of 25 each: three experimental groups (TENS, AUSSIE, IFC) and a sham group. Blocked randomization was done using www.random.org. Allocation was revealed just before the intervention. Participants received verbal and written explanations of the study's objectives and methodology and signed informed consent forms approved by the local ethics committee (CAAE 62256516.2.0000.0030) and registered in clinical trials (RBR-74ffv8) (Cuschieri, 2019)

Blinding

The researcher who applied the ES and the participants were blinded to treatment allocation. For this, another researcher performed the programming of each ES tested and placed a black cover on the ES device panel to maintain the parameters blinded for the researcher and the participants, except for the intensity current.

Participants

Participants were recruited through local clinics and hospitals via advertisement flyers. To be eligible for participation, participants should show both symptomatic and radiographic indications, as per the Kellgren-Lawrence scale, with a minimum grade of 2 (indicating at least mild radiographic osteoarthritis), observed in at least one knee compartment. In order to be eligible for the study.

Participants had to be 60 years or older, engage in at least 45 minutes of moderate physical activity per week, and report pain intensity of 4 cm or more on a 10-cm visual analogue scale. Exclusion criteria included recent physiotherapy (last 3 months), knee injections (past 6 months), medical conditions such as cardiorespiratory, neurological, or rheumatological dysfunctions, previous hip, knee, or ankle surgery, and chronic conditions causing knee pain.

Intervention

ES groups

Participants were randomized into three experimental groups: 1) TENS: pulse frequency of 100 Hz with a 200 μs of phase duration; 2) IFC: burst frequency of 100 Hz and carrier frequency of 4000 Hz (10 ms of burst duration and 10ms of duty interval) with a 125 μs of phase duration; 3) Aussie: burst frequency of 100 Hz and carrier frequency of 4000 Hz

(4 ms of burst duration and 16 ms of duty interval) with a 125 µs of phase duration (Table 1 for further details).

NMES was applied 12 sessions to the more affected knee only in an air-conditioned room controlled at 21°C (± 2). The therapist explained that the intervention consisted of ES applied to the more affected knee for 20 minutes. Participants were positioned in four points around patella with volunteer in dorsal decubitus with their legs extended and relaxed.

Four self-adhesive electrodes (25 cm² each) were placed around the patella. Two channels of the electrical stimulation equipment were used: Channel 1 had electrodes near the medial condyle of the femur and head of the fibula, and Channel 2 near the lateral condyle of the femur and the medial region of the tibial plateau. The goal was pain relief rather than muscle contraction. Patients provided feedback on the sensory perception of ES and allowed intensity increases until reaching maximum tolerated discomfort. Intensity was gradually raised every 5 minutes to maintain the sensory threshold. Each intervention group received 12 sessions of 20 minutes each.

Sham group

Participants received a current with a pulse frequency of 100 Hz with an intervention duration of 19 minutes and 20 seconds and 40 seconds of sham intervention for 12 sessions, as previously described (Zeng et al., 2015).

Outcome measures

All the outcomes were measured by the same blinded assessor before and after intervention (12 sessions), the main outcome measures included in this study and the recommended estimate of the minimum clinically important difference for each outcome

measure. We measured knee superficial temperature, pain intensity, and knee range of motion (with and without pain).

Primary outcome

Primary outcome was pain intensity assessed using a visual analogue scale (VAS). This self-reported pain score is a valid and reliable measure among people with KOA (Hawker et al., 2011). Ten centimeters graded scale was shown to the individual and he/she was asked about his/her pain, considering 0 as no-pain and 10 as the worst pain. Pain intensity was measured in 5, 10, 15 and 20 minutes of treatment and a follow up 30 minutes after the end of the treatment.

Secondary outcomes

Superficial knee temperature

Superficial knee temperature was measured as a surrogate for knee surface inflammation (Denoble et al., 2010; De Marziani et al., 2023)We captured three images of the lateral, medial, and frontal regions of the knee, and the average temperature in these three images was used. Superficial knee temperature was measured within 5, 10, 15, and 20 minutes of treatment, as well as a follow up of 30 minutes after the end of treatment.

A real-time thermal imager with a 640 x 480-pixel resolution was used to measure temperatures from -20°C to +1200°C. The device had a sensitivity of 0.08ºC and an accuracy within ±2ºC (Flir C2™, Wilsonville, Oregon, USA). Thermal analysis focused on the mean temperature from three knee images, captured using FLIR Thermal Studio Suite™ software. The mean temperature measurement showed excellent intra-rater reliability (intraclass correlation coefficient = 0.906 [0.87–0.93; 95% confidence interval]).

Data collection occurred every five minutes during treatment and 30 minutes post-treatment to monitor ES's physiological effects. A 0.5°C reduction in knee temperature was considered the minimum clinically important difference for KOA studies.(Denoble et al., 2010).

Painless range of motion (PROM)

For the assessment of PROM, a goniometer was employed. A trained examiner, following prior training, positioned the goniometer aligned with the lateral condyle of the femur and instructed participants to extend the knee until reaching the tolerable pain threshold(Epskamp et al., 2020).

Pressure Pain threshold

Using a pressure algometer (Kratos DDK, São Paulo Brazil), twelve knee points were assessed by a trained examiner (K.P). The algometer was positioned upright at each point and pressed until the participant first perceived pain. The points were:

P1: 2 cm below the medial epicondyle of the femur.

P2: 2 cm below the lateral epicondyle of the femur.

P3: 2 cm above the base of the patella.

P4: Center of the patella.

P5: 1 cm beyond the medial margin of the patella.

P6: 1 cm beyond the lateral margin of the patella.

P7: 2 cm below the medial margin of the patella.

P8: 2 cm below the lateral margin of the patella.

P9: Midpoint between the apex of the patella and the tibial tuberosity.

P10: Posterior point of the femoral epicondyle.

P11: 5 cm distal to the tuberosity of the lateral humeral epicondyle.

P12: 5 cm distal to the tibial tuberosity.

Three measurements were taken at each point with a 1-minute interval between them, and the mean of these three measures was used for data analysis.(Mutlu and Ozdincler, 2015)

WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index)

The WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) was assessed before and after twelve intervention sessions. WOMAC is a self-administered tool evaluating pain, stiffness, and physical function in hip or knee osteoarthritis patients. It can use a 5-point Likert scale, an 11-point numerical rating scale, or a 100-mm visual analogue scale (VAS). Within each dimension, specific questions gauge the severity of the condition. For pain, there are five questions about pain during activities like walking on a flat surface, climbing stairs, nighttime pain, sitting or lying down, and standing upright. There are two questions for stiffness and seventeen questions for physical function. Responses to each question are scored and aggregated to calculate subscale scores for pain, stiffness, and physical function, with an overall WOMAC index providing a measure of disability. (Roos, 1999)

SF-36

The SF-36 questionnaire is a generic health assessment tool that generates scores across eight scales, each measuring a distinct health concept, including physical functioning, role limitations due to physical or emotional issues, bodily pain, vitality, mental health, social functioning, and general health perception. Responses are recalibrated so higher

values indicate better health within each scale, and these values are then summed and transformed into a 0-100 scale using a specific algorithm, with higher scores indicating a better quality of life. The SF-36 also includes a separate single-item measure of health transition not used in scoring the multi-item scales.

Validated for use in Brazil (Laguardia et al., 2013), the SF-36 can typically be completed in about 10 minutes. Recently, the developers introduced algorithms to compute two summary measures: the Physical Component Summary Scale Score (PCS) and the Mental Component Summary Scale Score (MCS). These summary scores offer enhanced precision, reduce the need for numerous statistical comparisons, and address the floor and ceiling effects observed in some of the subscales.

TUG (timed up and go)

Timed Up and Go (TUG) test assesses functional mobility by measuring the time required for individuals to complete a sequence of tasks. This includes standing up from a chair, walking a distance of 3 meters, turning around, returning to the chair, and sitting down again. Patients are informed about the test before it begins, and they wear comfortable shoes during the assessment. The average time from three trials of the test is calculated in seconds. Importantly, all measurements are conducted consistently by the same investigator to maintain accuracy and reliability**.** (Alghadir et al., 2015)

30 seconds chair stand test (30CST)

The 30-second Chair Stand Test (30cst) was conducted using an approximately 45 cm high chair without arm support. Participants were encouraged to perform as many stands as possible within a 30-second timeframe. The test began with the participant sitting on the chair. A stand was counted if the participant rose fully (with straight hips and knees)

and then returned to a sitting position. Throughout the test, participants kept their arms folded across their chest.

Pain intensity was assessed before and immediately after the test (pain intensity during testing) using a numeric rating scale (NRS) ranging from 0 to 10, where 0 represents no pain and 10 represents the worst imaginable pain. (Gill et al., 2022)

Six-minute walk test (6MWT)

Participants were instructed to walk as quickly as they could for a duration of 6 minutes. They traversed back and forth along a 50-meter corridor, and the primary outcome measured was the total distance covered within the time frame. If necessary, participants were allowed to use crutches or walking sticks during the test. The assessment was performed before and after intervention. (Ateef et al., 2016)

Stair test (ST)

A stairway consisting of 11 steps, each with a height of 17 cm, was utilized for the study. Participants commenced with both feet on the bottom step, then ascended and descended the stairs as quickly as possible, before stopping with both feet back on the bottom step, optionally using the handrail for support. Timing commenced upon the start signal and concluded when participants returned with both feet on the ground. Total time was recorded to the nearest hundredth of a second. The assessment was performed before and after intervention. (Gkrilias et al., 2018)

40 meters fast walk test

A distance of 40 meters was measured using a tape measure. The participant was asked to walk fast as possible, and the time taken to cover this distance was recorded in seconds.

NRS was measured before and after test. This assessment was repeated before and after intervention. (Master et al., 2021)

Biodex balance system

Balance was assessed using the Biodex Balance System, which measures balance variability through standard deviation (SD). This system is designed for dynamic balance assessment, featuring a closed-chain, multiaxial platform interfacing with dedicated software (Biodex, Version 1.08, Biodex, Inc.). The platform includes an unstable circular balance surface capable of simultaneous movement along the anterior-posterior (AP) and medial-lateral (ML) axes. Key measurements provided by the system include the overall stability index (OSI), AP stability index, and mediolateral stability index. (Samina Javed et al., 2020)

Statistical analysis and sample size

The quantitative variables to characterize the sample are respectively expressed as mean and standard deviation (SD) or frequency distribution. The Levene test detected a normal distribution for the majority of variables. Accordingly, parametric statistics were mainly performed. All outcomes (primary and secondary) were assessed by two-way ANOVA with “time” (six levels: pre, 5, 10, 15,20 minutes and 30 minutes post intervention for pain and temperature. Three levels: pre, 20 minutes and 30 minutes after the end of intervention) and “groups” (four levels: TENS, IFC, Aussie, and Sham) as factors. Post hoc analyses (Bonferroni test) were performed when appropriate. Effect sizes were determined using partial eta squared ($\eta\rho 2$) for ANOVA. The Cohen’s d was used for the effect sizes and provided benchmarks to define small ($\eta\rho 2 = 0.01$), medium ($\eta\rho 2 = 0.06$), and large ($\eta\rho 2 = 0.14$) effects (Lakens. 2013).

The statistical software used was SPSS statistical software™ (version 20; IBM Corp., Armonk, USA). For all tests, significance level was set at p <0.05. Missing data for outcome measures were imputed using the expectation-maximization method (da Silva Almeida et al, 2022). The sample size was calculated based on the mean score on VAS for pain reported previously for a similar population of KOA patients (8.10 ± 1.23 cm) (Shimoura et al, 2019). An assumption was made that a clinically significant change in VAS scores would have to correspond to 30% of the total value, and a significance level of 0.01 and 95% power was chosen. These criteria led to an estimated minimum sample size of 25 in each group (Shimoura et al, 2019).

Results

Primary outcomes

In the pain outcome, there were significant differences (P<0.05) in the results among the treatment groups. In the TENS group (n=25), the mean difference in pain was -4.281 (3.43 to 5.12). In the IFC group (n=25), the mean pain difference was -5.26 (6.10 to -4.41). For the AUSSIE group (n=25), the mean pain difference was -4.40 (-5.24 to -3.55). In the SHAM group (n=25), the mean pain difference was -4.02 (-4.87 to 3.18). However, there was no significant difference (P<0.05) observed between the groups.

Secondary outcomes

Regarding knee surface temperature, the mean difference was 0.44 (-0.42 to 1.31) in the TENS group (n=25). In the IFC group (n=25), the mean difference was 0.05 (-0.81 to 0.92). For the AUSSIE group (n=25), the mean difference was 0.23 (-0.63 to 1.10). In the SHAM group (n=25), the mean difference was 0.36 (-0.50 to 1.23). No difference was found between groups for this outcome (P<0,05).

In the Free pain range of motion (FPROM) outcome, there were variations observed among the treatment groups. In the TENS group (n=25), there was a mean increase of 9.20 (-14.04 to 4.35). For the IFC group (n=25), the mean difference was 7.71 (2.87 to 12.57). In the AUSSIE group (n=25), the mean difference was 1.48 (-2.80 to 5.78). In the SHAM group (n=25), the mean difference was 4.00 (-0.83 to 8.84).

In the Total range of motion (TROM) outcome, results also varied among the groups. In the TENS group (n=25), there was a mean increase of 3.69 (-7.99 to 0.59). For the IFC group (n=25), the mean difference was 4.56 (0.27 to 8.86). In the AUSSIE group (n=25), the mean difference was -2.05 (-3.15 to -0.96). In the SHAM group (n=25), the mean difference was 2.79 (-1.50 to 7.08).

The Timed Up and Go (TUG) and VAS TUG outcomes also showed variations among the groups. For TUG, the TENS group (n=25) had a mean difference of -14.23 (0.57), while the IFC group (n=25) had a mean difference of -1.13 (-2.23 to -0.39). The AUSSIE group (n=25) had a mean difference of -1.95 (-3.04 to -0.85), and the SHAM group (n=25) had a mean difference of -1.79 (-3.20 to -0.39). Regarding VAS TUG, the TENS group (n=25) had a mean difference of -4.05 (0.64), the IFC group (n=25) had a mean difference of -0.51 (-1.92 to 0.89), the AUSSIE group (n=25) had a mean difference of -1.86 (-3.27 to -0.45), and the SHAM group (n=25) had a mean difference of 1.58 (0.40 to 2.77).

The Chair stand test (CST) and VAS CST outcomes also displayed variations among the groups. In CST, the TENS group (n=25) showed a mean difference of 8.44 (0.55), while the IFC group (n=25) had a mean difference of 2.02 (0.83 to 3.21). The AUSSIE group (n=25) had a mean difference of 0.65 (-0.53 to 1.83), and the SHAM group (n=25) had a mean difference of 1.58 (0.40 to 2.77). Regarding VAS TSL30, the TENS group (n=25) had a mean difference of -5.75 (0.52), the IFC group (n=25) had a mean difference of -

0.38 (-1.87 to 1.11), the AUSSIE group (n=25) had a mean difference of -1.52 (-3.01 to -0.02), and the SHAM group (n=25) had a mean difference of -1.46 (-2.92 to 0.03).

The Climb Stair test and VAS Climb stair test outcomes also showed variations among the groups. In ST, the TENS group (n=25) had a mean difference of 80.29 (4.05), while the IFC group (n=25) had a mean difference of -10.36 (-16.43 to -4.29). The AUSSIE group (n=25) had a mean difference of -2.60 (-4.12 to -1.08), and the SHAM group (n=25) had a mean difference of -10.56 (-16.63 to -4.49). Regarding VAS ST, the TENS group (n=25) had a mean difference of -6.08 (0.47), the IFC group (n=25) had a mean difference of -2.12 (-3.64 to -0.60), the AUSSIE group (n=25) had a mean difference of -2.60 (-4.12 to -1.08), and the SHAM group (n=25) had a mean difference of -2.47 (-3.99 to -0.95).

The 40-Meter Fast-Paced Walk Test (40M-FPWT) and VAS 40M-FPWT outcomes also displayed variations among the groups. In TC40M, the TENS group (n=25) had a mean difference of 33.63 (1.57), while the IFC group (n=25) had a mean difference of -3.56 (1.59 to 5.52). The AUSSIE group (n=25) had a mean difference of -3.54 (-5.51 to -1.58), and the SHAM group (n=25) had a mean difference of -2.74 (-4.10 to -1.38). Regarding VAS TC40M, the TENS group (n=25) had a mean difference of -4.92 (0.51), the IFC group (n=25) had a mean difference of -2.39 (-3.75 to -1.03), the AUSSIE group (n=25) had a mean difference of -1.69 (-3.05 to -0.33), and the SHAM group (n=25) had a mean difference of -1.82 (-3.79 to 0.14).

The 6-Minute Walk Test (6MWT) and VAS 6MWT outcomes also showed variations among the groups. In 6MWT, the TENS group (n=25) had a mean difference of 29.66 (12.48 to 46.84), while the IFC group (n=25) had a mean difference of 27.36 (10.18 to 44.54). The AUSSIE group (n=25) had a mean difference of 10.65 (-6.52 to 27.83), and the SHAM group (n=25) had a mean difference of 8.34 (-8.83 to 25.52).

For pain pressure threshold (PPT) no normal distribution was found for this data, so a normalization of data was made. For all the 11 points located in knee, groups TENS and IFC presented a pain reduction of 49.73% and 65.47% respectively. For all the other points, including P11 which is not located in knee (lateral epycondile) the reduction of pain was next to 20%.

The data for all secondary outcomes are available on *Supplementary material 1*.

Data analysis for PPT was made using a variation percentage between measures pre and post intervention, considering that this data did not attended the requisition of normal distribution in Kolmogorov-smirnov statistic test. Data for this outcome are available in TABLE 1.

TENS		IFC		AUSSIE		SHAM	
POINT	**VARIATION**	**POINT**	**VARIATION**	**POINT**	**VARIATION**	**POINT**	**VARIATION**
P1	-7.45%	**P1**	2.24%	**P1**	22.33%	**P1**	25.23%
P2	49.73%	**P2**	65.47%	**P2**	0.36%	**P2**	25.23%
P3	22.41%	**P3**	15.75%	**P3**	33.53%	**P3**	17.32%
P4	22.47%	**P4**	21.91%	**P4**	33.81%	**P4**	20.84%
P5	20.55%	**P5**	18.52%	**P5**	39.33%	**P5**	16.67%
P6	18.56%	**P6**	25.29%	**P6**	28.81%	**P6**	27.31%
P7	30.82%	**P7**	22.60%	**P7**	38.82%	**P7**	22.96%
P8	24.32%	**P8**	19.77%	**P8**	29.96%	**P8**	12.99%
P9	30.36%	**P9**	16.37%	**P9**	30.73%	**P9**	11.44%
P10	8.99%	**P10**	21.64%	**P10**	53.43%	**P10**	22.01%
P11	20.36%	**P11**	21.19%	**P11**	24.87%	**P11**	17.85%
P12	-3.82%	**P12**	14.12%	**P12**	35.99%	**P12**	10.71%

Table 2 Variation calculated by percentage of PPT outcome for all groups

Overall, although small statistical differences ($P<0.05$) were found in post-hoc tests, the study results indicate that regular electrotherapy sessions effectively reduce pain, improve functional test performance, reduce stiffness, and increase quality of life, with no significant difference compared to the SHAM group. However, balance, pain threshold, pressure, and temperature were not affected by electroanalgesia. These findings suggest that electrotherapy may offer specific improvements in pain and functionality without negatively impacting other sensations and physical parameters.

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PRODUTOS DESENVOLVIDOS NO PERÍODO DO MESTRADO

Manuscritos

- AZEVEDO, Klaus Porto et al. Different Cryotherapy Modalities Demonstrate Similar Effects on Muscle Performance, Soreness, and Damage in Healthy Individuals and Athletes: A Systematic Review with Metanalysis. Journal of Clinical Medicine, v. 11, n. 15, p. 4441, 2022.
- "SHORT-TERM EFFECTS OF SINGLE ADMINISTRATION OF ELECTRICAL STIMULATION WAVEFORMS ON PAIN, RANGE OF MOTION AND SKIN TEMPERATURE IN KNEE OSTEOARTHRITIS: A DOUBLE-BLINDED CLINICAL TRIAL" Manuscrito submetido na revista Frontiers in Physiology.

- **Produto de Impacto Social:**

  Palestrante na “I visitação de estudantes do ensino médio ao LaPlast e LAM”