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STUDY PROTOCOL

High and low frequency TENS in young people with primary dysmenorrhea: Clinical trial protocol

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Abstract

Background: Primary dysmenorrhea (PD) is lower abdominal pain in the absence of an organic cause, common in women under 25 years of age. It is the main cause of school/work absenteeism and presenteeism, therefore, the objective of its treatment is to provide women with adequate pain relief. Pharmacological treatment is characterized as first line, however it is associated with side effects. Transcutaneous Electrical Nerve Stimulation (TENS) is a non-pharmacological and non-invasive complementary therapy for pain management. **Objective:** To compare the effectiveness of high frequency (HFT) and low frequency (LFT) TENS modalities in relieving pain in young people with PD. **Methods:** Randomized, controlled and double-blind clinical trial protocol, with young women between 15 and 29 years old, nulliparous, regular menstrual cycle, self-report and presence of PD with pain intensity greater than or equal to three points on the Numerical Assessment Scale (Numeric Rating Scale - NRS). TENS will be randomized into two groups – Group HFT and Group LFT, application of 30 minutes, evaluated over the 24 hours after the intervention, for one menstrual cycle. In analyzing the results, the primary outcome will be the report of pain intensity. Secondary outcomes will be the durability of TAF and TBF analgesia; patient satisfaction and the presence of adverse effects; compare the amount of analgesic intake in the groups; assess the level of physical activity; evaluate the interference of PD symptoms in physical, mental and social activities and verify their interference with school/work presenteeism. **Considerations:** The present protocol aims to establish an evidence base for optimal recommendations on the use of TENS modalities for the relief of PD in young women.

Keywords: Dysmenorrhea; TENS; women's health; clinical trial protocol.

BACKGROUND

Primary dysmenorrhea (PD) has important implications for a woman's life course. It is characterized by pelvic pain and is one of the leading causes of absenteeism and presenteeism at school and work, with significant academic and socioeconomic impacts. Although considered a chronic health condition, it is still underdiagnosed, undertreated, and even underestimated by women themselves, who accept it as part of the menstrual cycle[1-6]. Pharmacological treatment is considered the most effective; however, it is associated with undesirable side effects, such as indigestion, headaches, and drowsiness. Therefore, it is interesting to integrate complementary and alternative, non-invasive therapies to alleviate adverse reactions at the critical moment of PD, such as the use of Transcutaneous Electrical Nerve Stimulation (TENS)[4,6-9].

TENS involves electrical stimulation of the skin through different currents and frequencies, providing an analgesic effect. The categorization of its frequencies is low-frequency TENS - LFT (1 to 10 Hz) and high-frequency TENS - HFT (50 to 150 Hz); both follow analgesic theories, one of which would be the increased release of endogenous opioids in the spinal cord and brainstem, such as endorphins, enkephalins, and dynorphins.

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In TBF, the activation of μ-opioid receptors would occur, while in HFT, the activation of δ-opioid receptors would occur[4,5,10–12]. Some systematic reviews and meta-analyses analyzed the efficacy of TENS in relieving pain and improving quality of life in women with PD. They found that although different parameters were used, HFT was statistically more effective than placebo TENS in reducing pain, but with similar results to LFT[4,5,13]. Given the above, and to create an evidence base for ideal recommendations for the use of TENS modalities for women with PD, the following question arises: is HFT as effective as LFT in relieving pain in young people with PD?

METHODS

Study design and ethical aspects:

The study is a randomized, controlled, double-blind clinical trial. The project was submitted to the Brazilian Registry of Clinical Trials (REBEC) and approved under identification number RBR-10n3h7vz, following the recommendations of CONSORT (Consolidated Standards of Reporting Trials). It was approved by the Ethics Committee for Research Involving Human Beings of the University of Pernambuco (Universidade de Pernambuco – REITORIA - UPE), and registered under CAAE number 57777522.3.0000.5207. The study will be conducted at the Women's Health Research Laboratory - LAPESM, located on the Petrolina campus of the University of Pernambuco (UPE).

Participants

Young women aged 15 to 29 years old, living in the Vale of São Francisco region (Brazil), who have self-reported and present PD, that is, who have pain in the pelvic or lower abdominal region, occurring from 48 hours before the start of the menstrual period to 72 hours after the first day of menstruation, with an intensity greater than or equal to 3 points on the Numeric Rating Scale (NRS), will be included in the study[14]. In addition, they must be nulliparous and have a regular menstrual cycle. Women who are pregnant or breastfeeding, who use any type of intrauterine device, who have skin lesions in the area where the electrodes will be placed, who are suffering from self-reported neurological or cardiac diseases, and women diagnosed with gynecological disorders that may be associated with secondary dysmenorrhea, such as endometriosis, adenomyosis, uterine fibroids, among others, will not be allowed to participate in the study and will be excluded.

It is important to note that women who undergo care or interventions during the course of the research will not be excluded, but the practices performed by them will be recorded in the participant's medical records. Likewise, any signs of skin irritation, intolerance, or discomfort associated with electrostimulation will also be recorded.

To calculate the sample size, the results referenced by the study by Bai, et al. (2017)[1] will be used, regarding the effect of TENS for pain relief in women with PD, using a mean outcome of 1.9 in the experimental group, 0.5 in the control group and a standard deviation of 2.5, with a power of 80%, a significance level of 5% and a percentage of 20% of losses or withdrawals, totaling a sample of 150 participants, with each group having 75.

Recruitment and randomization

Recruitment will take place through the dissemination of the project in health services, through local advertising (radio, newspaper advertisements and companies), on social media, invitations by e-mail, direct contact with participants of previous studies and verbal dissemination carried out through Health Education on Premenstrual Syndrome and PD.

Those interested in participating in the study should contact the cell phone number, also WhatsApp, provided at the time of the dissemination. On this occasion, women will receive a link that will be made available by the researchers evaluating the study, containing a Google form with some questions regarding the study's eligibility criteria.

Immediately after confirming eligibility, women will receive prior guidance regarding the research objectives and procedures, and must sign the Free and Informed Consent Form (FICF). Those under the age of eighteen must sign the Free and Informed Assent Form (FICF) and the Free and Informed Consent Form of the Guardian (FICF).

Eligible women will be randomized through a simple randomization sequence that will be created on the website randomization.com, by a researcher who will not be involved in any stage of the study. Distribution into groups will occur individually through sealed, opaque and numbered envelopes that will be opened in front of the participants by a member of the team not involved in the study's evaluations or interventions. Participants may be proportionally assigned to one of two experimental groups: High Frequency TENS Group (GTHF) or Low Frequency TENS Group (GTBF).

Intervention protocol:

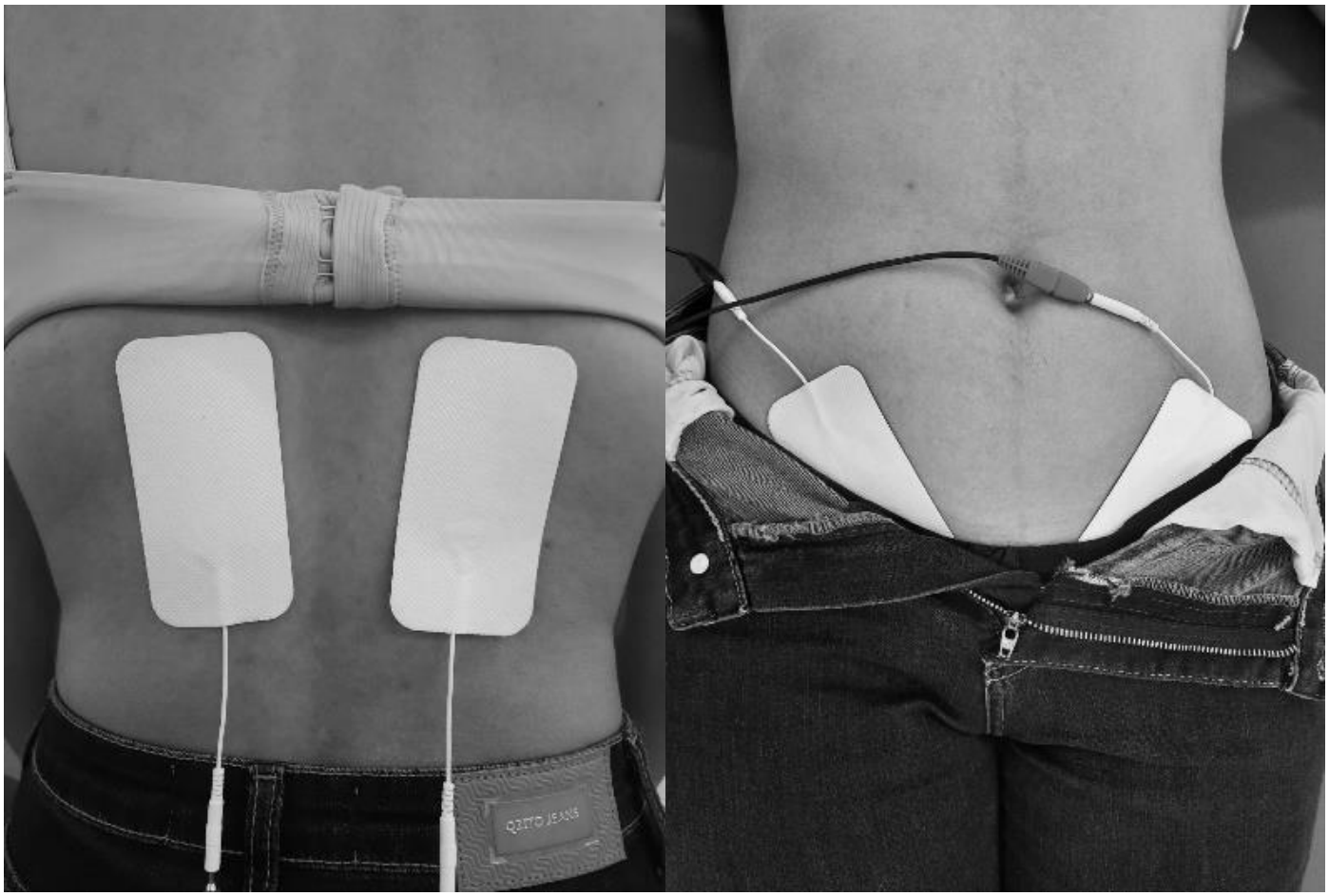
Women will be treated and receive the intervention in a single menstrual cycle when they report the presence of pain greater than or equal to 3 on the Numerical Rating Scale[14] and will be monitored for the following 24 hours after the intervention of a TENS session. Health Education information regarding the nature and coping of PD will be provided to both groups.

The leading researchers, evaluators, and interventionists will be blinded to the groups' allocation, definition, and intervention. The interventionist researchers will be trained to adjust the intensity parameters and apply TENS safely and effectively. To ensure that both the interventionists and the participants are blinded, the devices' displays will be covered to prevent recognition of the intervention.

The entire intervention protocol will be structured and based on the production of scientific evidence found in the literature under the guidance of the Guidelines for the Application of Sensory-Level TENS for Primary Dysmenorrhea[5].

TENS

First, the participant's skin will be inspected and cleaned with 70% alcohol to reduce impedance. Immediately afterward, a pair of self-adhesive electrodes will be placed in the thoracic region of T10 - T11, as these are areas related to the spinal nerve roots that receive nociceptive information from the uterus, and the other pair will be placed in the dermatomes corresponding to the referred pain, more specifically, medially in the lower abdominal quadrants, in the suprapubic region (Figure 1).



A) B)

Figure 1. Positioning of the electrodes.

Note: A) Pair in the thoracic region at T10-T11. B) Pair in the suprapubic region of the lower abdominal quadrants.

The women will be instructed to lie on dorsal decubitus position during the treatment. The device used in this study will be the IBRAMED brand - Neurodyn portable (IBRAMED, Brazilian Industry of Medical Equipment EIRELI), with two channels - TENS, made of metal and polypropylene, bivolt (automatic), with 100-240v input, with frequency parameters of 50-60hz, output of 09 volts, with ANVISA Registration: 10360310012 and self-adhesive electrodes (5 X 10 cm).

For women allocated to the HFT group, a biphasic pulse waveform will be adjusted, with a frequency of 100Hz, a pulse duration of 100μs, and the highest intensity level tolerable by each participant, assessed every five minutes and with continuous adjustment of the current amplitude so that an intense sensation is felt throughout the intervention. The LFT group will have the same parameters defined for the HFT group, except the frequency, which will be adjusted to 4Hz. The duration of the treatment for both groups will be 30 minutes.

Assessment of results:

During the research, participants will undergo assessments at three different times (Figure 2).

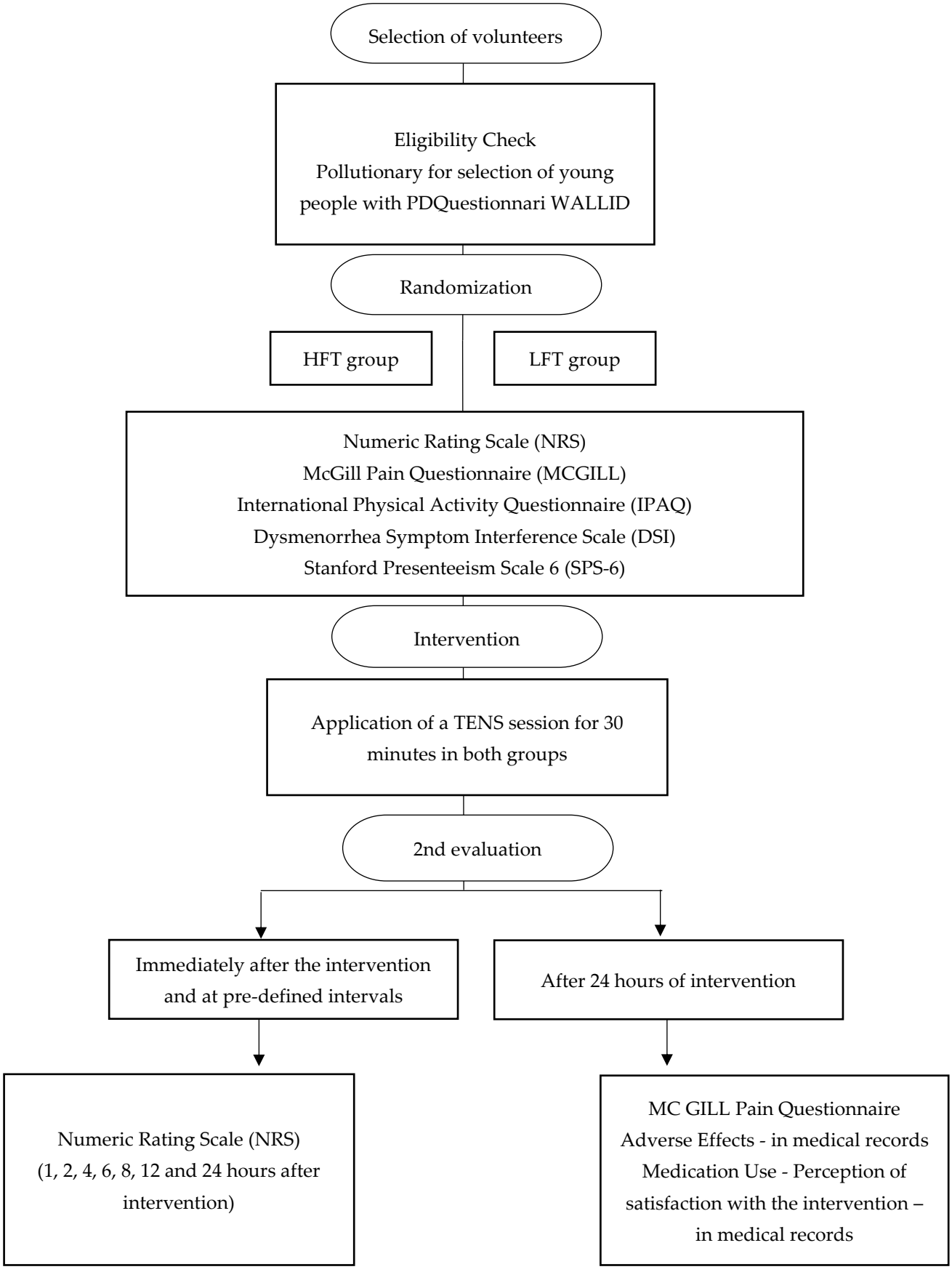


Figure 2. Flowchart of operationalization of the study

All eligible women will be instructed to answer a questionnaire to collect baseline information to characterize the sample, with basic information such as sociodemographic data, gynecological, obstetric, and anthropometric data, and health history. At this time, information will also be collected regarding health status, sexual life, menstrual history, functional assessment, and application of the Working Ability Location Intensity Days of Pain Dysmenorrhea (WaLIDD), a questionnaire with the ability to diagnose PD and predict sick leave, composed of a scale that integrates characteristics of dysmenorrhea such as anatomical locations of pain, the amplitude of pain, number of days with pain during menstruation and frequency of disabling pain to perform activities. Each variable assessed by the WaLIDD instruments ranges from 0 to 3, and its final score ranges from 0 to 12 points, as follows: 0 no dysmenorrhea, 1-4 mild dysmenorrhea, 5-7 moderate dysmenorrhea, 8-12 severe dysmenorrhea[15].

It is important to note that if the volunteer is not experiencing a painful menstrual cycle at this first contact, only the eligibility check and baseline data collection will be performed. The woman will be instructed to wait for the next painful cycle so that the intervention and investigation for the study can be carried out.

In the second stage, after randomization and before the intervention, validated questionnaires will be applied to measure the study variables. The Numeric Rating Scale (NRS) and the McGill Pain Questionnaire - A short version will be used to assess pain; the International Physical Activity Questionnaire (IPAQ) to assess the level of physical activity; the Dysmenorrhea Symptom Interference Scale (DSI) to determine the interference of PD symptoms in the physical, mental and social activities of the participants; and the Stanford Presenteeism Scale 6 (SPS-6) to assess presenteeism with PD.

The final assessment will be carried out over the next 24 hours following the intervention using an individual medical record that will be applied by the evaluating researchers via WhatsApp. The women will be asked about pain, the occurrence of adverse effects, the need to use medication, and their perception of satisfaction with the intervention's effect using a likert-type scale.

Primary outcome

Self-reported pain intensity

Pain will be assessed from the first contact with the participant until 24 hours after the intervention. The NRS is a short, easy-to-administer, and validated tool for measuring known pain intensity in populations. Its scale ranges from 0 to 10, where 0 = no pain; 1 - 3 = mild pain; 4 -6 = moderate pain; 7 - 9 = severe pain; and 10 = the worst pain imaginable[16]. First, it will be applied before the intervention, immediately after, and 30 minutes after completion. Then, the NRS will be applied at predetermined intervals after the single TENS session: 1, 2, 4, 6, 8, 12, and 24 hours.

The McGill Pain Questionnaire will be used twice to assess pain in its subjective aspects, first before the use of TENS and then 24 hours after the treatment. Its abbreviated version has 15 items divided into two dimensions, one sensory with 11 items and the other affective with four items. The questionnaire also includes one more item to assess the intensity of current pain and a visual analog scale to assess the intensity of pain in recent days[17].

Secondary Outcomes

Level of physical activity

By using the short version of the IPAQ, it will be possible to verify the level of physical activity of the women participating in the study. This questionnaire can estimate the time spent performing physical activities during the week, in days and minutes, grading them into four levels of intensity: very active - met the recommendations and performed an activity: a) vigorous for a time ≥ 5 days/week and ≥ 30 minutes per session or b) vigorous for a time ≥ 3 days/week and ≥ 20 minutes per session + moderate and walking for a time ≥ 5 days/week and ≥ 30 minutes per session), active - met the recommendations and performed an activity: a) vigorous for a time ≥ three days/week and ≥ 20 minutes per session or b) moderate or walking for a time ≥ 5 days/week and ≥ 30 minutes per session, or c) any activity added together that results in a time ≥ 5 days/week and ≥ 150 minutes/week - walking + moderate + vigorous); irregularly active - considered as someone who performs physical activities with insufficient frequency and duration to be classified as active, and can be divided into two groups: a) has a frequency of 5 days/week or a duration of 150 min/week, and b) did not meet any of the recommended criteria regarding frequency or duration; and sedentary - did not perform any physical activity for at least ten continuous minutes during the week. The IPAQ assesses physical activities in different contexts, such as work, transportation, household chores, leisure, and passive activities[18].

Symptom interference

The DSI will be used to assess the interference of PD symptoms in women's physical, mental, and social activities. This self-administered instrument, specific for cyclical menstrual pain, can be used in women of different ages, levels of education, professional status, and pain intensity[19].

The DSI consists of 9 items with the following response options: 1 - Not at all, (2) A little, (3) Moderately, (4) Enough, and (5) Excessively. Its final score is obtained by calculating the average of the individual items, which can be used as long as at least 5 of the nine items are answered. Higher scores reflect a more significant interference of symptoms associated with PD in the lives of women affected[19].

Presenteeism

The SPS-6 is a self-administered questionnaire developed to verify the relationship between presenteeism, health problems, and productivity at work[20].The present study will measure how much the pain caused by PD interferes with the items assessed by it.

Each of the six items of the SPS-6 has a Likert-type scale, which ranges from 1 (completely disagree) to 5 points (completely agree), with the ability to measure concentration and work performance despite the health condition presented. Of the six items, questions 1, 3, and 4 are part of the group of questions that address psychological factors and the ability to maintain concentration while performing work, while questions 2, 5, and 6 are part of the group related to the interference of the health problem presented in the performance and achievement of goals at work, generally associated with physical causes[20,21].

The total score of the instrument varies between 6 and 30 points and is calculated by adding the points of each item. It should be noted that for psychological aspects, the worst score considered is "1 - I completely agree," for physical causes, the worst condition is

associated with the answer "5 - I completely disagree". Lower scores between 6 to 18 reflect a reduction in the performance of work activities, and higher scores indicate better performance at work[21].

Duration of analgesia, Presence of adverse effects, and use of medication

An individual electronic medical record will be used during the 24 hours following the TENS intervention to monitor possible adverse effects, use of medication, and duration of the analgesic effect. The adverse effects investigated will be those related to, for example, sensations of muscle vibrations, tightness, headaches, mild burning or redness.

The use of medication will be verified to determine whether its intake was necessary, and if so, information regarding the type and quantity ingested will be collected. The duration of the analgesic effect will be assessed through the perception of satisfaction with the impact of the intervention. After 24 hours, women will be instructed to answer the following questions: "TENS was effective in relieving menstrual pain" and "I am satisfied with the intervention to relieve menstrual pain." For both questions, the response options will be on a Likert scale, with the following response options for the first question: (1) Not at all effective; (2) Somewhat practical; (3) Moderately effective; (4) Effective and (5) Very effective", and for the second question: 1) I disagree entirely; (2) I disagree; (3) I am indifferent (or neutral); (4) I agree and (5) completely agree.

Statistical Analysis

The statistical analysis will be performed by a statistician who is blind to the group allocation and is not involved in the research. The data obtained through the questionnaires and scales will be tabulated in an Excel 2010 spreadsheet. The statistical analyses will be performed using the Statistical Package for the Social Sciences version 22 (SPSS Inc., Chicago, IL, United States of America, Release 16.0.2, 2008). Before analyzing each variable, the normality of the data distribution will be verified using the Kolmogorov-Smirnov test. A descriptive analysis of the continuous variables belonging to the study will be performed using measures of central tendency (mean and median) and measures of dispersion (minimum and maximum value, standard deviation). Categorical variables will be analyzed using absolute and relative frequencies.

The association of dependent variables will be performed using the Spearman or Pearson correlation coefficient test. The mean difference in the effects of the interventions and the difference between the groups will be calculated using mixed linear models with unstructured covariance involving the treatment groups, time (follow-up), and the interaction between the groups over time. All analyses will be performed according to the intention-to-treat principle. Multiple imputation procedures will be adopted and defined as a posteriori to deal with potential problems of missing data. In all analyses, a P value <0.05 will be considered.

CONCLUSION

The present protocol aims to compare the effects of high-frequency TENS with low-frequency TENS and establish an evidence base for optimal recommendations on the use of TENS modalities to relieve PD in young women.

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Conflict of interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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