****** Disclaimer: This document is a direct translation of the original protocol of the research proposal titled "***El uso de la música para el manejo del dolor por dismenorrea primaria en estudiantes de la Escuela de Medicina y Ciencias de la Salud de la Universidad del Rosario***". The protocol was submitted to Universidad del Rosario´s Institutional Review Board in Spanish, as per of their requirements. The research protocol was approved by the IRB on July 18, 2017 at the Capital District of Bogotá, Colombia under the identification number DVN021-1-099-CEI856. Footnotes have been added in parts that had changes. Principal Investigator Juan S. Martin-Saavedra, MD, did the translation of the document. Communications with the IRB and the approved informed consent used were not translated but if required please request to the principal investigator. ******

GENERAL INFORMATION

ORIGINAL TITLE (in Spanish): El uso de la música para el manejo del dolor por dismenorrea primaria en estudiantes de la Escuela de Medicina y Ciencias de la Salud de la Universidad del Rosario

TITLE: Music listening for the management of pain in primary dysmenorrhea of students from the School of Medicine and Health Sciences, Universidad del Rosario

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RESEARCH GROUP: Clinical Research Group
ORGANIZATION: School of Medicine and Health Sciences, Universidad del Rosario

SETTING: Bogotá D.C., Colombia

RESEARCY TYPE: Clinical Trial
LAST EDITED: April 20, 2017

SUMMARY

Primary dysmenorrhea is described as a crampy-like pain in the lower abdomen that occurs during menses. It is estimated as one of the most common pathologies in women of reproductive age. Nonetheless, it has been suggested as under-diagnosed and under-treated. Currently, the first line of management is the NSAIDs (Non-Steroidal Anti-inflammatory Drugs) and the OCC (Oral Contraceptives). Nevertheless, the effectiveness

is below 100%, and contraindications, as well as adverse effects, exist. Music effectiveness in pain relief has been reported in different clinical context and is recommended as a complementary therapy for pain management. However, music has not been studied for pain relief in primary dysmenorrhea. The following project pretend to study the efficacy of music for pain relief in primary dysmenorrhea, in students from the School of Medicine and Health Sciences, Universidad del Rosario, Capital District of Bogotá, Colombia. This document proposes the conduction for a single blinded and randomized clinical trial. Participants would be allocated through computer randomization one of two groups. The experimental group would be exposed to a song composed by one of the investigators, and it will be compared to a silence group used as control. It is expected to identify a significant reduction in pain perception in primary dysmenorrhea in the experimental group compared to the control group.

PROJECT DESCRIPTION

1. Research question conception and justification

Dysmenorrhea comes from the Greek words *dys* "hard or painful", *men* "month or monthly", and *rrhea* "discharge" (1). Dysmenorrhea is defined as painful menses, and is characterized by a crampy-like pain that locates in the lower abdomen. It is classified as primary or secondary dysmenorrhea (1-4). Primary dysmenorrhea may be defined as colic, or spasm, located at the lower abdomen during menses, that is not associated to any pelvic or uterine pathology (2, 4). The onset usually occurs during the first 24 months after menarche (1, 2). The pain begins some hours prior or after menses (1, 4), and it lasts between 8 to 72 hours, with the most sever symptoms during the first or second day of menses (1, 2).

Primary dysmenorrhea is considered the most common gynecologic condition in women of reproductive age (2-4). Some studies have reported that dysmenorrhea has a negative impact of quality of life (2, 3), and is considered the first cause for school and work absence in these women (2, 4).

First line of management is Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). Second line of management is Oral Contraceptives (OCC) or other forms of hormonal contraception (2-7). Nonetheless, efficacy of the treatment with NSAIDs and OCC is no under 100% (2, 4). Other types of treatment include: transcutaneous electrical nerve stimulation, nitroglycerin patch, and laparoscopic sacral and uterine nerve ablation (2, 4). Other described treatments include: acupuncture, local heat, herbal beverages, massage, music listening, and others (1).

The International Association for the Study of Pain (IASP), defines pain as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage", and includes primary dysmenorrhea in the classification of chronic pain syndromes (8). Pain is a complex experience (9), and its complexity has motivated the study of complementary treatments for pain management such as music (10-19). However, to date, no studies on the effectiveness of music for pain relief in primary dysmenorrhea have been conducted.

- Research questions:

    a) Could music improve the overall painful experience in primary dysmenorrhea?

    b) Could music be used as an alternative therapy for pain relief and reduce the analgesic requirements in primary dysmenorrhea?

    c) Could music, unknown to the patient, be able to effectively relieve acute pain in primary dysmenorrhea?

- Project justification

About 116 million of people suffer from any form of chronic pain (a prevalence that surpasses the prevalence of diabetes, cancer, and hypertension together) according to the Institute of Medicine (IOM) of the United States. Chronic pain is considered a disease and an epidemic. Additionally, 60% of the visits to the emergency department are for acute pain, and of those, 74% are of moderate to sever pain (9).

Since 1994, the IASP included dysmenorrhea as a chronic pain syndrome (8), and as a pelvic chronic pain syndrome (2, 20). Firs line of management for primary dysmenorrhea includes NSAIDs and OCC (2, 4, 20). Due to the little knowledge on these drugs and the disease, the inadequate formulation, the self-formulation, the adverse effects, and the contraindications; primary dysmenorrhea is currently under treated with an efficacy below 100% (2, 4). This has increased the use of non-pharmacological treatments as complementary therapies (1, 2, 4). However, better knowledge on this forms of treatment are needed, which supports the conduction of proper clinical trials.

- Background

Prevalence of Dysmenorrhea in College and High School

Prevalence of dysmenorrhea varies a lot in the literature (2, 4, 21). Several studies of the prevalence and characteristics of dysmenorrhea among College students (1, 3, 22-24) and High School students exist (25, 26). Prevalence in non-college students has been reported of 72% in Japan (26) and 85% in Hispanic population of the USA (25). The prevalence in college students has been reported of 62,4% in Mexico (22); 45,3-87,7% in Turkey (1, 3, 23); and 86.4% in Jordan (24).

In Colombia, Yañez et al. reported that the prevalence in students from Medicine and Psychology, from Universidad del Rosario during the year 2010. Mean age was 19.3 years (SD 2.8), and the results reported a prevalence of 73% (n=92 of 126), from which, 96.7% reported the pain was of 3 or more on a VAS (severe to moderate). Additionally, 91.3% of the students used a drug, of which, 66.7% were self-formulated (27). This study shows the high prevalence of this pathology in the target population of this research.

Currently, dysmenorrhea is diagnosed clinically (5-7) but the definition changes among different authors (2), which explains the variability in the prevalence. Other important

issues that may explain this are the life style among women. Different life styles seem to affect the symptoms in dysmenorrhea (2, 5-7). For example, several authors agree that exercise is associated with a smaller prevalence (1, 4, 7). Also, a diet rich in Omega-3 seems to be associated to a smaller prevalence (4, 7). Additionally, some identified risk factors are tobacco use, and family history of dysmenorrhea among other (2, 4-7).

Physiopathology

The most accepted physiopathology of dysmenorrhea involves the over production of arachidonic acid derivate, especially prostaglandins (PG) (2, 4, 8, 28). Increase in PG of patients with dysmenorrhea have been reported, mainly PGE_2 and $PGF_{2\alpha}$ have been associated with it (2, 4, 28). Other molecules, such as Leukotrienes $LT\text{-}C_4/D_4$ and LTE_4 (4, 24), nitric oxide (4), and vasopressin (2, 4), seem to be associated. Nonetheless, the better understood are the PG, and direct association between concentrations of PG and the severity of dysmenorrhea have been reported (2, 4).

It is accepted that the increase in PG induce hyper contractility of the uterus, which in consequence produce a blood flow fall and transitory ischemia during each contraction (2, 4, 28). At the end of menstrual cycle, endometrial tissue is torn and PG are therefore secreted (2). Right before ovulating phase, there is an increase in phospholipids with Omega-6-like chains (e.g. arachidonic acid), and occurs at the time when progesterone decreases (4, 28). Progesterone decrease seems to stabilize lizosomes that are rich in PG in the uterus (2, 28).

Some physiologic differences have been described between women suffering from dysmenorrhea, and those that not. Women suffering from primary dysmenorrhea usually have higher uterine tone at steady and active states; they have a higher contractile frequency, and a more irregular uterine contractility. Molecular studies have reported an increase in the expression of pro-inflammatory genes in patients with dysmenorrhea. Moreover, it has been suggested that hormonal patterns also differ among these patients (2).

Treatment

As mentioned, NSAIDs, are the first line for the management of pain in dysmenorrhea, nevertheless, the effectiveness is reported between 64 to 100% (2, 4). Inadequate use of these drugs has been reported (4), and about a 15% of patients do not respond to NSAID treatment (2, 4). It has also been described that 54% of adolescents identifies the drugs that can be used for dysmenorrhea, and about 28% do not recognize a NSAID among three types of drugs (4).

Inadequate use of NSAIDs requires stratification of cardiovascular, renal and gastric risks. NSAIDS should be avoided in hepatic failure, stage 3 renal disease or with any kidney disease. They should also be avoided in peptic disease, peptic ulcer, and inflammatory bowel disease (29). At the moment, no evidence exist indicating a superior NSAID (4, 29). Regarding oral contraceptives (OCC), meta-analysis have shown that long term use of OCC is associated to thromboembolic events (28, 30). Other forms of analgesic treatments have been described among women suffering of dysmenorrhea (1, 2, 28).

A recent study evaluated the characteristics of primary dysmenorrhea in college students, and they also evaluated their knowledge and usage of complementary forms of therapy (non-pharmacological). This research included 488 students from University of Manisa Celal Bayar of Turkey, and 87.7% reported to suffer dysmenorrhea. From those, 80.9% reported suffering from a moderate (4-7.9 in a VAS) to severe (8 to 10) pain. Additionally, they found that only 55.1% any kind of analgesic, while 72.2% used any form of non-pharmacological therapy (1).

Other authors have also reported that 98% of women have used at least one form of complementary therapy, however, effectiveness has been perceived of about 40% (2, 4). The most commonly described and used methods include local heat (known by 82.1% and used by 85.7%), taking a shower (87.6% and 79.2%), and massages (76.6% and 59.6%). Music is described as known by 43.5% but used only by 31.3% (1). Several authors have referred that some habits such as doing exercise (1, 4), diets rich in omega-3 (4, 28, 29), and vitamin B1, vitamin E, and drinking ginger tea have been reported to be effective, but more studies are still needed (28). On the other hand, doing exercise and local heat patches have shown the largest evidence of its analgesic effectiveness (2, 28).

Neurologic changes in patients with primary dysmenorrhea

It has been suggested that the repetitive exposure to painful stimuli induces a central sensitization (2, 31). Central sensitization is defined as an augmented response to painful stimuli (hyperalgesia), or to non-painful stimuli (alodinia) (2, 31, 32). It is described as neuronal plasticity event that occurs secondary to the exposure to painful stimuli (32).

In 1944, Haman, did the firs study that described hyperalgesia in patients with dysmenorrhea (33). Later on, several studies have reported mixed results (2, 31), however, some authors included dysmenorrhea as a central sensitization syndrome (31). It has been suggested that the mixed results are due to methodological differences such as the painful stimuli used, and the menstrual cycle phase studied (2, 34). On recent research evaluated pain perception secondary to cervical distention, finding that higher perception to the painful stimuli during the follicular phase in women with primary dysmenorrhea compared to those without the diagnosis (35). Other study reported higher perception to deep muscular pain, induced through injection of saline solution, during the three cycle phases (menstrual, luteal and follicular) in patients with severe dysmenorrhea (34).

Several authors have also described an association between primary dysmenorrhea and higher incidence of chronic pain syndromes such as irritable bowel, bladder pain syndrome, and fibromyalgia among others (2, 31, 36). It has been suggested that this higher incidence in patients with dysmenorrhea is due to mal-adaptive changes at the central nervous system (2, 36). In 2015, Wei et al., found differences in brain connectivity between the periaqueductal gray matter (PAG) with dorso- and mediolateral regions at prefrontal cortex of women with a 9 year history of dysmenorrhea (36).

Music as a non-pharmacological analgesic

It has been reported that music activates several and different central nervous system structures (37-49). Some these, are cortical areas that are related to pain perception such as primary somatosensorial cortex, insulae, and cingulate cortex (37, 39, 40). It has also

been reported activation of subcortical areas that participate in descending modulation of pain (39, 40), including the PAG and dorsolateral prefrontal cortex (40). This supports a neuromodulator effect by music-induced analgesia rather than a simple distraction, making music a more appealing intervention for pain relief in pathologies such as dysmenorrhea.

Between 2004 and 2015, six systematic reviews (10-15) and four meta-analyses (16-19) evaluating the efficacy of music listening for pain relief were identified. Three of these revisions described a significant effect in postoperative pain (11, 12, 14), and the meta-analysis by Hole et al., reported a mean pain reduction of 23mm on a VAS (19). One meta-analysis evaluated oncologic pain (18), one evaluated rheumatologic pain, specifically in fibromyalgia and ostoartritis (15), and one meta-analysis evaluated pain in endoscopic procedures (colonoscopy, endoscopy, others); all of these reported a significant effect by music. Two revisions included different types of pain and also identified a significant effect (10, 13). Only one review did not find significant effects. The review by Bechtold et al. evaluated the effects of music in pain associated to colonoscopy, not finding any significant difference (16).

It is important to note that Cepeda et al., Tsai et al., and Hole et al., identified large heterogeneity between their included studies due to different clinical settings, different populations, and different music interventions (13, 18, 19).

The effect of music in analgesic requirements has also been evaluated. Some of the aforementioned reviews found significant reductions (13, 17, 19). Nonetheless, results by Bechtold et al. found no differences (16). Among the other reviews, two described varied results (11, 12), and four did not evaluate the analgesic requirements (10, 14, 15, 18).

Regarding the use of music in gynecologic pain, Cole et al. included in their analysis studies in labor pain and a study on pain in cesarean section, finding significant effect in both (19). Since 2004, several publications on gynecological pain have been published. One evaluated pain in surgical abortion (41), four studied pain after cesarean section, (42-45) and three assessed labor pain (46-48). Excluding the research on surgical abortion (41), and one on pain in cesarean section (46), all studies describe significant reductions of pain in those that listened music (42-44, 47-48). Despite that music has shown effectiveness in gynecologic pain, and some referring pain in dysmenorrhea to be similar to labor pain (3, 4); results are can´t be extended to women suffering from dysmenorrhea and studies directly evaluating this conditions are required.

2. Objectives:

2.1. General objective

To evaluate the efficacy of a receptive music intervention compared to a control group exposed to silence, on the painful experience in primary dysmenorrhea in college students 18 years or older from the School of Medicine and Health Sciences, Universidad del Rosario, Bogotá D.C., Colombia.

2.2. Specific objectives

- To describe demographic, medical history, gynecologic and obstetric history of the studied population.
- To describe the analgesic strategies and drugs used for pain relief in primary dysmenorrhea in the studied population.
- To evaluate the quantified perception of usual pain in primary dysmenorrhea using a VAS in college students 18 years or older.
- To explore if a difference exist in the acute quantified perception of pain in primary dysmenorrhea, using a VAS, among 18-year or older college students prior to receive the music or silence interventions.
- To evaluate if a difference exist in the acute quantified perception of pain in primary dysmenorrhea, using a VAS, among 18-year or older college students after receiving the music or silence interventions.
- To explore if a difference exist in the change of quantified pain perception using a VAS in primary dysmenorrhea, from the moment prior to the intervention until the moment after the intervention, among 18-year or older college students that listened to music or stayed in silence.
- To evaluate if a difference exist in the acute quantified perception of pain in primary dysmenorrhea, using a VAS, among 18-year or older college students 3 to 6 hours after receiving the music or silence interventions
- To explore if a difference exist in the change of quantified anxiety in primary dysmenorrhea, evaluated with the Zung's scale, from the moment prior to the intervention until the moment after the intervention, among 18-year or older college student that listened to music or stayed in silence.
- To evaluate if a difference exist in requirements of pharmacological analgesics for pain relief in primary dysmenorrhea, among college students that received music compared to those that stayed in silence after the intervention, and 3 to 6 hours after the intervention.
- To evaluate if differences exist in heart rate, systolic blood pressure, and diastolic blood pressure, using a calibrated digital sphygmomanometer, between 18-year or older collge students receiving music and those staying in silence.

3. Material and Methods

Design

A prospective and single blinded randomized clinical trial will be conducted. Two groups will be compared, the experimental group will receive a music intervention, and control group will stay under the same condition and the same time with headphones in silence.

Study population

Female students 18 years or older matriculated to one of the programs registered at the School of Medicine and Health Sciences from Universidad del Rosario. Students volunteering to participate, those giving written consent to participate in this protocol, and those complying our eligibility criteria:

- Inclusion criteria

1. Students at least 18 years old.

2. With legal and cognitive capacity to give written consent to participate.
3. Patients that comply to characteristics and definition of primary dysmenorrhea according to literature (2, 4-8):
    a. Crampy-like pain located in the inferior abdomen, lumbar region, or inguinal region
    b. Pain initiating no longer than 24 hours prior to the first bleeding during the menstrual cycle
    c. Pain lasting 24-72 hours
    d. Pain that always occurs with menses
4. Ability to understand and respond all questionnaires and measuring tools.

- Exclusion criteria

1. Prior diagnosis of endometriosis, adenomiosis, myomatous uterus, or any other gynecologic cause of secondary dysmenorrhea.
2. Any degree of hearing impairment or use of auxiliary hearing devices.
3. Diagnosed cognitive deficit or neurologic condition.
4. Prior diagnosis of psychiatric disease, use of anxiolytic or anti-depressive drugs, or history of substance or alcohol abuse in the last two years.
5. Diagnosis of cancer, diabetes mellitus, or cardiac disease.
6. Advanced music training (receiving advanced music theory in adition to normal music education given by schools).
7. Irregular menstrual cycles.
8. Diagnosis of any endocrine disease.
9. Current use, or use in the last two months, of oral contraceptive or other hormonal contraceptive method.
10. Prior gestation or labor.

Variables and measurement tools:

- **Demographic data:** age, current studying semester, religion, and civil status will be collected.
- **Medical history:** medical, surgical and obstetric history will be collected.
- **Menstrual cycle data:** the following will be collected: 1. Menarche; 2. Time between each cycle; 3. Menses duration; 4. Contraceptives use.
- **Pain associated to menses:** using a visual analogue scale (VAS), the usual pain associated to menses will be collected. The VAS useas a 10 cm line that that goes from 0 “I have never felt pain during my menses” to 10 “I always feel the worst of pain of my life during menses”.
- **Strategies used for pain relief:** simple questions will be used to ask drugs and dosis used for pain relief, and non-pharmacological treatment use.
- **Pain intensity:** a VAS will be used to measure pain intensity during menses. The following question will be used “How intense is your pain at this moment?” where 0 is “I do not feel any kind of pain” and 10 is “I am feeling the worst pain of my life”.
- **Anxiety:** a 10 item short version of the self-applied scale for the measurement of anxiety by Zung will be used (49). Zung´s scale was developed in 1971 (50), it is of free use, and has been studied and validated in Spanish and in colombian population (49, 51). De la Ossa et al., evaluated internal consistency and functional structure of the original scale compared to a 5 item and 10 items short versions, finding high consistency for all three especially for the 10-item version (49). The short version

consist of items 1, 2, 3, 4, 6, 7, 8, 11 and 15 (Supplement 5). Each item has 4 possible answers (never, some times, most of the time, all the time), and the patient should only give one per item.

- **Acute analgesic requirements:** the following questions will be used: 1. ¿In this moment would you like to take any kind of drug for pain relief? If the answer is yes, the generic name of the drug will be asked.
- **Analgesic requirments during the day**: a collecting item that requests the following: 1. Drug name; 2. Drug presentation; 3. Dose used; 4. Time for using the drug.
- **Vital signs:** using a calibrated sphygmomanometer the following will be measured: systolic blood pressure, diastolic blood pressure, mean blood pressure, and heart rate. Blood pressure will be measured at level of the radial artery of the dominant arm. Measurement will be done with the patient sitting and with the arm extended at the level of the heart window.

Procedure

An open enrollment will be offered to all female students of at least 18 years old from the School of Medicine and Health Sciences from the university. The researchers will approach students that want to participate at any moment, and eligibility criteria will be assessed using a simple questionnaire based on inclusion and exclusion criteria.

The study will be explained in detail to the students that are found to be eligible. A speech will be design prior to enrollment to avoid disclosing different information among participants. The speech will mention that: "…they will participate in a research about the effects of music in primary dysmenorrhea, in which they will be compared to a control group…"[1]. The speech will explain the rest of the details for the experimental part of the study. Finally, they will be requested to sign informed consent for participation.

After signing informed consent, patients will be allocated by computer generated randomization. Randomized codes will be generated and information about the study will be put in envelops. The information inside the envelope will not disclose the allocated group.

The intervention will be conducted after pain associated to menses begins. The information in the envelopes will contain instructions for the intervention. These will explain how to access the intervention, additionally, it will contain information on what to do while enrolled to the study. The patient will be instructed to avoid taking drugs or doing any analgesic therapy before receiving the allocated intervention. Nevertheless, it will be clarified to the patient that she can do any form of analgesia if needed but it should be informed to researchers. The intervention will be avoided if patients have to endure pain for 12 hours or more, or those that use any form of analgesia before the intervention. Both of these will be clearly instructed to participants. Patients that can't receive the interventions due to the afore-mentioned situations will not be excluded as they can receive the intervention at any other menstrual cycle.

Patients will contact the researchers for the intervention, at that moment, patient will give the coded number and researchers will identify a package to give (package A or package

[1] ***[not in the original protocol] - Note: the final speech did not disclose the experimental group or the main outcome (pain) as requested by IRB for approval (communication DVN021-1-088 and approval communication DVN21-1-099-CEI856) - .***

B)[1]. The researcher that gives the package will not be involved in data collection nor will have knowledge of them. The other researcher will not know which package was given to the student. After receiving the package, the other researcher will guide the patient to the place where the intervention will be conducted.

Every package will contain an MP4 electronic device and a set of headphones. Packages will be identical and the music device will be set to look the same visually. The researcher will apply a first questionnaire to collect demographic data, medical history, surgical history, gynecologic and obstetric history, the first VAS evaluating usual pain (VAS1) in dysmenorrhea, and the first measurement of vital signs (all measurements will be collected according the explained protocol in the variables and measurement tool section). After this, another VAS evaluating acute pain (VAS2) and the short version of the Zung's anxiety scale will be collected.

The student will put on the headphones and the researcher will set the volume at 50 dB, and will play the file "AUDIO 1", and then he will leave the place. The volume is under security ranges stablished by Resolution 8321 of 1983 from the Ministry of Health from Colombia. This stablished that, the maximum level of sound intensity would be 105 dB for continuous expositions during 1 hour. The student should stay for 30 minutes listening to the AUDIO 1 file following the instructions of the package. The instructions will also explain to the patient that she can't mention what she listened through the headphones (during the intervention or even after it). Additionally, patient will be explained that she can't modify the volume during the 30 minutes. The patient is free to stop the device and the intervention but this should be informed to the investigator immediately. After the 30 minutes of the intervention the researcher will enter again the room.

After ending the intervention and entering back, the researcher will collect the following data: pain perception according to VAS (VAS3), anxiety using the Zung's scale, vital signs, and the patient will be asked if she desires to take any analgesia at that moment. Additionally, the patient will be given another questionnaire that includes: pain perception using a VAS (VAS4), anxiety using the short version of the Zung's scale, information about any drug or other form of analgesia used. This questionnaire should be answered by the student 3-6 hours after the intervention. This questionnaire should be delivered to the investigators. The patients will be able to bring with them any type of analgesic (the ones they usually used) and to initiate their usual analgesia after collection of variables post-intervention.
According to the objectives of this research, the intervention will be conducted in the first 12 hours of pain in dysmenorrhea. The first participants will be able to receive again the intervention, nevertheless, any additional data after the first intervention will not be considered for the main analysis of the study. Prior to initiating the protocol, the medical service from the Quinta de Mutis will be contacted and informed to assure adequate service for primary dysmenorrhea management for patients that request it or for those that need it during the intervention or after ending it.

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[1] ***[not in the original protocol] - Note: testing of the MP4 devices showed a sound artifact while playing any type of audio file. In consequence, the intervention was conducted using the same laptop for both groups, and blinding was done by external researchers of the School not related to this trial. This assured that investigators (JSMS and AMRS) where completely blinded of allocation as explained in the manuscript and in the final version of the protocol registered at ClinicalTrials.gov under the identification number NCT03593850 (all changes were approved by the IRB in the communication letter DVN21-1-099-CEI856) - .***

Music intervention

Both groups will receive their intervention in the same physical space that will be assigned by the School of Medicine and Health Sciences from Universidad del Rosario. The place will assure a calm environment without noise or interruptions by any situation external to the research. Both will receive the intervention in the same conditions.

Each group will receive the following intervention:

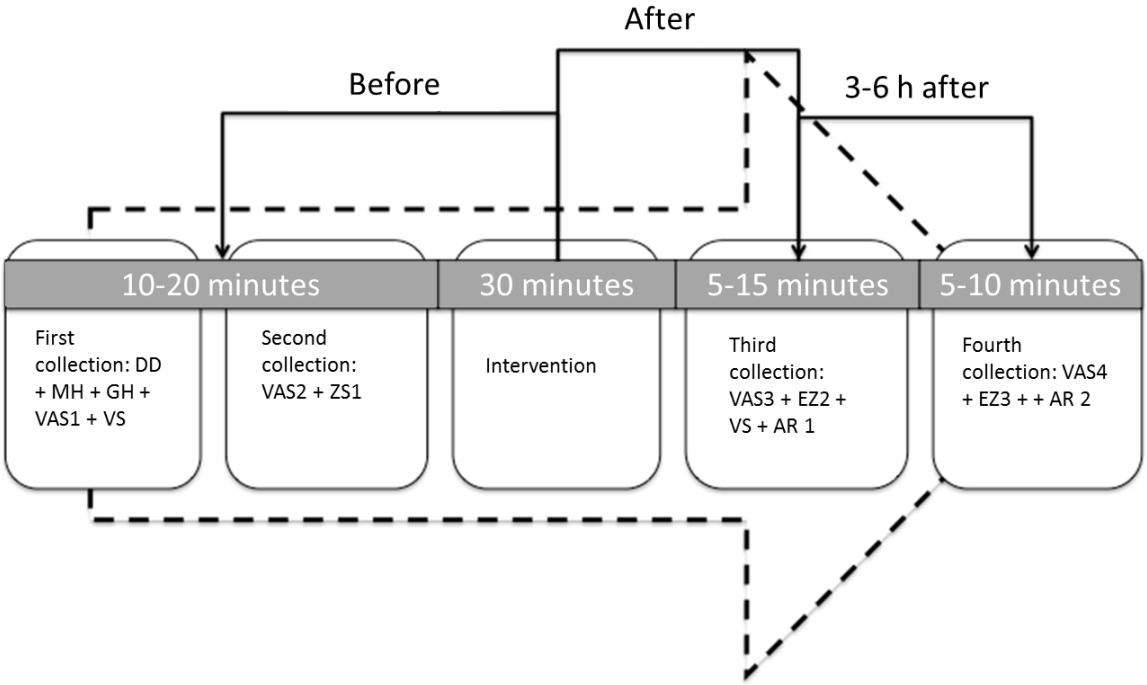
- Control group: an audio file named AUDIO 1 will be uploaded to the MP4 device. The file will be a 30 minute silence file. Students in the control group will be siting for 30 minutes with the headphones on and in silence.
- Experimental group: an audio file named AUDIO 1 will be uploaded to the MP4 device. The file will be a 29 minutes and 32 seconds in duration song. The song will be composed by the researcher Juan Sebastian Martin-Saavedra with the following characteristics: 1. Tempo 60-80 bpm; 2. The song will be composed on a C (Do) major scale and a 4/4 key signature for the entire musical piece, variations during the song will be made in the relative minor scale, A (La) minor; 3. The son will contain string and wind instruments, no percussion instruments, singing, lyrics, or vocalizations will be used for the song, additionally, synthesizers will be used. The music song will be organized in the following way:
    - Introduction
        - It will start with 45 second of complete silence. This way while the researcher leaves the intervention room, he won't be able to identify the allocated group.
        - Then, a synthesizer will play a C (Do) note in crescendo for 6 minutes and 11 seconds. At the same time melodic progressions with violin, cello, and clarinet will play.
    - Part I
        - First, the guitar (main instrument) will be introduced while playing arpeggios in a four chord sequence in C major. This segment will last about 2 minutes and 41 seconds.
        - After that, the guitar will play three different chord sequences: the first will be an 8 chord sequence in C major, followed by a 4 chord sequence in A minor, and will end with a 4 sequence in C major.
    - Part II
        - A 4 chord sequence in C major will start and then change to another 4 chord sequence in A minor (longest segment), and will finish in a 4 chord sequence in C major.
        - From the minute 28 and 25 seconds the final sequence will play again an arpeggio until ending in a decrescendo.
    - During parts I and II, the guitar will be accompanied all the time by the C note in the synthesizer, a bass melody, and in sporadic passages, melodies in violin, cello and clarinet. Every harmonic sequence in the guitar will be played in different styles used in rock, ballad, and bossa-nova.

It was decided to use a completely new song with the aim to identify if an exclusive analgesic effect by music exists. It has been suggested that music chosen by the patient has a larger anxiolytic and analgesic effect, however, two systematic review did not found significant differences in their statistical analysis (13, 19). Therefore, this methodology

was decided to further investigate if the election of music influences its effect in pain relief.

Data collection:

The following figure shows the different moments for data collection:



DD, demographic data; MH, medical-surgical history; GH, gyneco-obstetric history; VAS1, usual menses pain; VS, vital signs; VAS2, pain perception before the intervention; ZS1 anxiety before the intervention; VAS3, pain perception after the intervention; ZS2, anxiety after the intervention; AR1, analgesic requirements after the intervention; VAS4, pain perception 6 hours after the intervention; ZS3, anxiety 6 hours after the intervention; AR2, used drugs or other analgesic therapies up to 6 hours after the intervention.

Sample calculation:

Considering the objectives of this study, the main endpoint is the change in pain perception evaluated with a VAS. For the sample calculation a one sided alternative hypothesis, a significance level (*p* value) α of 0.01 and a power (1-β) of 0.90 (β=0.1) was stablished.

The following are the null hypothesis (H_0) and alternative hypothesis (H_1):

- H_0: no differences in the change of the acute pain perception (ΔP) in primary dysmenorrhea, from before the intervention (VAS2) until the moment after the intervention (VAS3), among the control (CG) and the experimental (MG) groups.

$$VAS2_{CG}\text{-}VAS3_{CG} = VAS2_{MG}\text{-}VAS3_{MG}$$

$$\Delta P_{CG} = \Delta P_{MG}$$

- H_1: Students listening to music (MG) will have a larger pain reduction (ΔP), from the moment before the intevention (VAS2) to the momento after (VAS3) the intervention, compared to silence group (CG).

- $VAS2_{CG}$-$VAS3_{CG}$ < $VAS2_{MG}$-$VAS3_{MG}$
- $\Delta P_{CG} < \Delta P_{MG}$

The prevalence of primary dysmenorrhea in the students from two programs (medicine and psychology) of the School of Medicine and Health Sciences from Universida del Rosario was described as 73%, with a mean pain intensity of 5.8 (SD 2.0) using a VAS (27). Nevertheless, no studies reporting the efficacy of music listening for pain relief in dysmenorrhea has been published, therefore there are no data regarding the change of pain intensity in the studied group. Moreover, the control group will wear headphones in silence while resting in the same conditions, this type of control (placebo) has not been described in the literature and won't allow an accurate sample calculation. Due to this, the first part of the study will be done as a pilot study for a better sample calculation.

Nonetheless, it was decided to review data in similar context to do an initial sample calculation before the pilot. As mentioned, menses pain has been compared to labor pain, therefore, three studies evaluating this pain were review (46-48). One research compared music against massage and a VAS of 6 points was used so it was not considered (46). One study compared music against control (usual care) (47), and the other compared against Hoku point massage and a control group (usual care) (48). Both studies were done in primiparous women, and pain was measured with a 0-10 point and no additional analgesia was received until the intervention (47-48). These studies reported a mean age of 26.63 (SD 4.02) years old (47); and 21.43 (SD 2.58) years old (48). If averaged, the age of the studies is 24.03 years old, similar to the mean age of our target population 19.3 (SD 2.8) (27).

The mean pain before the intervention, measured at 4 cm of cervical dilation, was 6.43 (SD 2.57) (47), and 5.58 (SD 1.29) (48). If both means are averaged, a mean perception is 6.01, which is similar to that of the target population (27). Mean score after the music intervention during the latent phase was 4.43 (SD 1.03) with a mean difference of -1.15 that corresponds to a 20% pain reduction. For the control group the mean before the intervention was 6.13 and after was 6.48 that corresponds with a mean difference of + 0.35 (increased). Comparing both differences, the change between groups was 1.58 supporting the music group (48). The other study (47) did not report mean pain scores after the intervention, but they did report a mean difference between groups of 1.68 supporting music group. Considering these reports, a mean difference between groups of 1.5 in pain relief supporting music group was established.

The following formula was used:

$$n= ((AR+1)/1) \cdot (Z[1-\alpha]+Z[1-\beta])^2 \cdot \sigma^2/\Delta^2$$

n= sample per group
AR (allocation rate) = 1
$Z[1-\alpha]= 2.33$
$Z[1-\beta]= 1.28$
$\sigma= 2$
$\Delta= 1.5$

According to this, n=46.34. In consequence, 47 students per group was calculated. After the pilot testing a new calculation will be done with more data obtained from the studied population and the interventions to study[1].

Data analyses

The SPSS for Mac, version 20, software was used for data analyses. For qualitative variables, frequency and percentages measurements will be used. For quantitative variables, central tendency measurements, variability and variance coefficients was used.

The primary endpoint for the study will be the effect of music in pain in dysmenorrhea. The secondary endpoints will be the impact in analgesic requirements, vital signs, and anxiety quantification. Comparative analysis will be performed to evaluate if a relationship between the level of pain and analgesic requirements, anxiety levels, and vital signs exist. Finally, multivariate analysis (MANCOVA) will be conducted to further test statistical significance for the pain relieving effect of music ($p < 0.01$).

4. Ethical considerations

This study is classified as minimum risk in accordance to the stablished regulations by the Resolution 008430 of 1993 from the Ministry of Health of Colombia (Scientific, technical, and administrative norms for the research in health).

All participants from the study will enroll and participate on their own desire and no perosn will be obligated to enroll, continue or complete the study participation. The study will not expose participants to drug interventions, surgical procedures or diagnostic procedures, physical therapy or other type of intervention that will add potential risks to physical integrity of participants. The study will be conducted in the Quinta de Mutis of the Universidad del Rosario, Bogota city. Therefore, no exposure to ambient risks will be related to this research. The sole intervention patients will receive is music through headphones. For conducting this research all recommendations from Helsinki declaration by the World Medical Associations will be considered.

5. Activity chronogram

	MES															
ACTIVITY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
PROTOCOL DEVELOPEMENT																	
SEARCH FOR ADDITIONAL FUNDING IF REQUIRED AND IRB SUBMISSION																	
DATA COLLECTION																	
DATA ANALYSES																	
PATIENT RECRUITMENT ACCORDING TO ELIGIBILITY CRITERIA																	

[1] ***[not in the original protocol] – Note: before doing the first intervention it was deemed more appropriate to perform an interim analysis than a pilot study -.***

INTERVENTION AND DATA COLLECTION FROM INCLUDED PATIENTS	
DATA ANALYSES	
DISCUSSION OF DATA ANLYSES	
COMPLETE RESULTS REPORT	
MANUSCRIPT PREPARATION	
SUBMISSION FOR PUBLICATION	
MANDATORY SOCIAL SERVICE DURATION	

6. Expected results

For our main objective, we expect to find a significant relief of pain perception in students with dysmenorrhea that listened to music. These results are expected to provide clin8ical evidence for a possible complementary therapy in the management of pain in dysmenorrhea, allowing to improve management of this condition and reduce analgesic drug requirements. Additionally, we expect to describe the prevalence, characteristics of pain and treatment strategies for dysmenorrhea used by the studied population.

The main benefits will be for the women of reproductive age, which are affected by the studied condition. Furthermore, healthcare providers and medicine will benefit. Identifying new forms of evidence based non-pharmacological therapies will allow physicians or other healthcare providers to treat pain, or similar conditions to dysmenorrhea, in a holistic way, avoiding pharmacological therapy abuse and to reduce pharmacological adverse events.

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PROJECTED BUDGET

Exclusive expenses that may be required for the research:

- Monthly salary for the physician in Mandatory Social Service as a research assistant for a 12 month period. The salary will be determined by the School of Medicine and Health Sciences.
- Four MP4 devices and four headphone set compatible to the devices.
- Calibrated digital sphygmomanometer. The School of Medicine and Health Sciences will be consulted to evaluate the availability of these instruments to be used for the study[1].

Total expenses associated to the research:

- Monthly cost: 2'467,000 COP.
- One-time costs: 240,000 COP (4 MP4 devices) + 170,000 (one new digital shpyngomanometer).

The following table provides the complete projected budget:

Categoría	Item	Valor Unidad	Pago	Cantidad	Duración (meses)	Total	Costo adicional requerido para el proyecto?
PERSONAL	Médico Social Obligatorio	2200000	Mensual	1	12	26400000	SI
PERSONAL	Investigador principal UR	15000000	Mensual	1	12	180000000	NO
MATERIALES	Reproductor MP4	60000	Único	4	12	240000	SI
MATERIALES	Tensiómetro + fonendoscopio	70000	Único	1	12	70000	SI
MATERIALES	Pulsoxímetro	90000	Único	1	12	90000	SI
SUMINISTROS	Material bibliográfico	YA SE TIENE				0	NO
SUMINISTROS	Costos publicación	1500000	Único	1	-	1500000	SI
SOFTWARE	SPSS para MAC	YA SE TIENE				0	NO
INSTALACIONES	Construcciones	NO SE REQUIEREN NUEVAS				0	NO
VIAJES	Viajes	NO SE REQUIEREN				0	NO
MATERIALES	Computador	YA SE TIENE				0	NO
COSTO TOTAL PROYECTO						208300000	
COSTO TOTAL ADICIONAL EXCLUSIVO DEL PROYECTO						28300000	

[1] ***[not in the original protocol] - Note: all tools (MP4 devices, laptop, and sphygmomanometer) were available at the School so no funding was required for the conduction of the trial -***

SUPPLEMENTS

SUPPLEMENT 1. FAST QUESTIONNAIRE: Eligibility criteria

Answer Yes or No

QUESTION	YES	NO
Are you 18 years or older?		
Do you suffer from crampy-like pain located in the lower abdomen associated to menses?		
Have you ever been diagnosed with any of the following: endometriosis, adenomyosis, myomatous uterus?		
Have you ever been diagnosed with hearing impairment or require the use of hearing devices)?		
Have you ever been diagnosed with Cancer, Diabetes, Cardiac disease, neurologic disease, or endocrine disease?		
Do you currently use or have used in the last two months oral contraceptives or other hormonal contraceptive method?		
Have you ever been diagnosed with any psychiatric condition or have you ever required psychiatric drug use?		
Have you ever received additional music education besides that provided in your school?		
Have you ever been pregnant?		

SUPPLEMENT 2. QUESTIONNAIRE: Demographic and personal data

Personal data

- Age:
- Studying program:
- Ongoing semester:
- Marital status :
- Have you ever received additional music education besides that provided in your school? (Select one) SI NO
    - If your answer was YES, please specify:
      _____

Medical History

Have you been diagnosed with any disease? YES NO

Specify: _____

Have you required surgery? YES NO

Specify:_____

Is there any important disease in close family member (father, brother, grandparents, uncles/aunts)? YES NO
Specify:_____

Have you suffered an accident? YES NO
Specify:_____

Gynecologic history

Please complete the following:

- Pregnancy:___ Losses (Abortions):___ Born children:___
- Age at menarche:
- How many days do you have your menses? _____
- How many days do your menses last? _____

Regarding the pain associated to your menses:

1. Which of the following describes better your pain? (Select one)
    a. Opressive (squeeze-like)
    b. Crampy (spasm)
    c. Burning (ardor)
    d. Other:_____
2. At what time do you start feeling pain? (Select one)
    a. 48-24 before my menses

b. < 24 hours before my menses
c. The same day of my menses
d. First 24 hours after my menses
e. Other:_____

3. How much time do you feel pain during your menses? (Select one)
   a. < 10 hours
   b. 10-24 hours
   c. 24-48 hours (1-2 days)
   d. 48-72 hours (2-3 days)
   e. Other:_____
4. Which was the first time you felt pain with your menses? (Select one)
   a. With my first menarch
   b. 1-6 months after my menarche
   c. 6-12 months after my menarche
   d. 1-2 years after my menarche
   e. Other:_____
5. Did you take any drug for pain relief during your last menses? YES NO
   Drug name:_____
   Used doses (Number of tablets):_____
   E.g. Ibuprophen 4 tablets of 800 mg
6. Did you use any form of non-pharmacological strategy for pain relief during your last menses? YES NO
   Specify:_____

For this part please read carefully instructions

Visual analoge scale (VAS) consist of a 10 cm line. The line is marked with a 0 in one side and 10 in the other, and consider 0 as the least possible intensity and 10 as the greatest. For using the tool you have to put a mark that represents the perceived intensity that better answers the question.

7. Consider 0 (I have never felt pain during menses) and 10 (I always feel my worst kind of pain). Which is your usual pain associated to menses?

SUPPLEMENT 4. Questionnaire for the day of the intervention

STUDIED VARIABLES

The following document will be of exclusive use for the researchers during the day that the study is conducted. TIME:_____

Please answer the following questions.

1. With a single mark plese answer. How much pain are you feeling right now? Consider 0 as "I'm not feeling any pain" y 10 "I'm feeling the worst pain of my life" (patient must answer by herself).

   0 _____ 10

2. Please answer the following questions with: Never, Sometimes, Most of the time o Always.

Question	**Never**	**Sometimes**	**Most of the time**	**Always**
Have you felt nervous or anxious lately				
Have you felt fearful lately				
Have you been irritated or have you panicked easily				
Have you felt down				
Have you felt tremulous				
Have you felt headache, pain on your back, or pain on your neck				
Have you felt weak and fatigue easily				
Have you felt palpitations or elevated heart rate				
Have you felt dizzy lately				
Have you felt nausea or stomack disturbances lately				

3. Answer Yes or No. Would you take an analgesic drug or other would you do another analgesic strategy at this moment? If Yes, please specify: _____

4. At this moment how much time have you felt pain?

5. HR___ BP___ MBP____

Please complete the following after the intervention.

1. With a single mark plese answer. How much pain are you feeling right now? Consider 0 as “I’m not feeling any pain” y 10 “I’m feeling the worst pain of my life” (patient must answer by herself)

   0 _____ 10

2. Please answer the following questions with: Never, Sometimes, Most of the time o Always.

Question	**Never**	**Sometimes**	**Most of the time**	**Always**
Have you felt nervous or anxious lately				
Have you felt fearful lately				
Have you been irritated or have you panicked easily				
Have you felt down				
Have you felt tremulous				
Have you felt headache, pain on your back, or pain on your neck				
Have you felt weak and fatigue easily				
Have you felt palpitations or elevated heart rate				
Have you felt dizzy lately				
Have you felt nausea or stomack disturbances lately				

3. Answer Yes or No. Would you take an analgesic drug or other would you do another analgesic strategy at this moment? If Yes, please specify::

   _____

4. HR___ BP___ MBP____

SUPPLEMENT 5. Data collection by the patient during the rest of the day

PAIN INTENSITY DURING THE DAY

This questionnaire is designed to be used by you (participant) 3 to 6 hours after having received the intervention. TIME:_____

Complete the following tables:

1. If you have taken any kind of analgesic drug please fill this table with the following information:

DRUG NAME	TIME	QUANTITY

2. If you have performed any form of non-pharmacological strategy for pain please fill this table with the following information:

USED STRATEGY	TIME	DURATION

Please answer after 3-6 hours have passed from receiving the intervention.

1. With a single mark plese answer. How much pain are you feeling right now? Consider 0 as “I’m not feeling any pain” y 10 “I’m feeling the worst pain of my life”. Please mark your answer on the line.

0 _____ 10

2. Please answer the following questions with: Never, Sometimes, Most of the time o Always.

Question	**Never**	**Sometimes**	**Most of the time**	**Always**
Have you felt nervous or anxious lately				
Have you felt fearful lately				
Have you been irritated or have you panicked easily				
Have you felt down				
Have you felt tremulous				
Have you felt headache, pain on your back, or pain on your neck				
Have you felt weak and fatigue easily				
Have you felt palpitations or elevated heart rate				
Have you felt dizzy lately				
Have you felt nausea or stomack disturbances lately				

SUPPLEMENT 6. Instructions to receive the intervention

INSTRUCTIONS FOR RECEIVE THE INTERVENTION

Thank you for participating in our study, please read carefully.

WHEN WILL I RECEIVE THE INTERVENTION?

When you **start feeling pain associated to your menses** the intervention will be able to be conducted. At this moment you should contact the researcher[1].
IMPORTANT: If it is not posible to receive the intervention **during the first 12 hours of pain**, the intervention will be avoided and it is recommended give your usual treatment to pain. If this happens, remember that **you are not excluded from the study** you would be able to receive the intervention in the next month.

AT WHAT PLACE WILL THE INTERVENTION TAKE PLACE?

The intervention **will be conducted at the facilities of the Quinta de Mutis** in an assigned place for it. The specific place **will be specified when you contact** the
At what time will the intervention take place?

The intervention will take place **from Mondays to Fridays 7:00 am – 5:00 pm,** nevertheless, you can contact the researcher to schedule the intervention outside of this time if needed.

Please consider the following

- No drug or other strategy should be used for pain relief until the intervention has been completed. Nonetheless, it is informed that **you are in full freedom to do it if needed** but it should be informed to the researcher. Please consider that **the intervention will not be conducted if you use any drug or other form of analgesic strategy** for pain relief PRIOR to receving the intervention. If this happens, you won't be excluded from the study and would be able to receive the intervention for the next menses.
- When you receiving the intervention, or after having received it, **you can't disclose to the researcher what you listened** through your headphones.
- If desired, **you can stop the intervention before completing the 30 minutes** but you have to inform the researcher who will enter and perform corresponding measurements.
- If you want to receive the interention again, you can request it but the new data of new interventions will not be considered for the analysis.
- Independent of the allocated group, **you can request to researchers the music file** used for this study.

[1] Contact information: juans.martin@urosario.edu.co/ cel: 3002230897/ PBX: 2970200 ext 3426