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ESCAPE pain trial - The effects of Curcumin in pain relief in women diagnosed with primary dysmenorrhea: A triple-blinded, placebo-controlled, phase II, randomized clinical trial protocol.

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Abstract:

***Introduction**: Primary dysmenorrhea affects many women, being a major cause of absenteeism and reduced productivity at work and at school. Although non-steroidal anti-inflammatory drugs (NSAIDs) are a good treatment option, up to 18% of women show no response or present allergic reactions and adverse events. Curcumin has antispasmodic, antinociceptive and both specific and nonspecific anti-inflammatory effects, with good tolerability and safety. To date, no previous trial involving curcumin and dysmenorrhea pain has been performed. Therefore, our main goal is to assess the efficacy of curcumin for pain relief among women with primary dysmenorrhea, along with determining curcumin's adverse effects and tolerability profile.*

***Methods:** A phase II, single-center, randomized, triple-blinded, placebo-controlled, parallel-group, superiority trial to evaluate the effect of curcumin (500 mg/12h) in pain reduction in women (18 to 35-year-old) with primary dysmenorrhea. A first cycle will be used for a passive, observational run-in phase. A sample of 108 participants (54 per group) is necessary to detect a 30% difference in pain sensitivity between groups assessed by visual analogue scale (VAS). Secondary outcomes include side effects, Cox Menstrual Symptom Scale (CMSS), and use of rescue drugs for pain relief.*

***Discussion**: Clinical evidence has shown analgesic and anti-inflammatory effects of curcumin and in view of dysmenorrhea's physiopathology being related to those mechanisms targeted by curcumin, we hypothesize its use could represent an innovative and effective therapy to reduce the severity of this disease and its symptoms.*

***Keywords:** primary dysmenorrhea, Curcumin, pain relief, Visual Analogue Scale, Cox Menstrual Symptom Scale.*

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ABBREVIATIONS
NSAIDs: Non-steroidal anti-inflammatory drugs
VAS: Visual Analogue Scale
CMSS: Cox Menstrual Symptom Scale
COX: Cyclooxygenase
PG: Prostaglandins
PMS: Premenstrual Syndrome
GILZ: Glucocorticoid-Induced Leucine Zipper
IWRS: Interactive Web Response System
DCC: Data Coordination Center
NF-kB: Factor nuclear kappa light-chain-enhancer of activated B lymphocytes

INTRODUCTION

Dysmenorrhea (menstrual pain) is a condition that affects almost half of reproductive-aged women (Zondervan et al., 2001). It can be classified as primary (no visible cause) or secondary (related to a specific pelvic disease: endometriosis, leiomyoma, adenomyosis, among others). Primary dysmenorrhea occurs in 50% of young women during ovulatory cycles and is usually limited to the first 48 or 72 hours of menstruation (Dawood, 1990).

Pain in primary dysmenorrhea is caused by a prostaglandin-dependent mechanism (Maia et al., 2005). During menses, progesterone and estradiol decrease, while a simultaneously increased expression of endometrial collagenases, metalloproteinases, and pro-inflammatory cytokines lead to a breakdown of the endometrial tissue (Oladosu et al., 2018), followed by a release of phospholipids, which later generate prostaglandins (PG), prostacyclins, and thromboxane A2 via cyclooxygenase 1 and 2 (COX 1 and 2) enzymes (Oladosu et al., 2018; Dawood, 2006). PG acts on nociceptors and stimulate uterine contractility, causing cramps (Dawood, 2006). Prostaglandin E2 (PGE2) and Prostaglandin F2 alpha (PGF2α) levels are higher in women with dysmenorrhea compared to healthy women (Oladosu et al., 2018).

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit PG synthesis and reduce uterine contractility (Chan,1983). Although they are considered one of the best treatment options for the disease (Milsom, I., & Andersch, B., 1984) approximately 18% of women affected do not respond to NSAIDs (Oladosu et al., 2018), due to impaired uterine perfusion, leading to hypoxemia and ischemia of the smooth muscle (Dmitrović, 2000) and polymorphisms in the genes that encode for COX1 and COX2 enzymes (Weng et al., 2013). Some women present allergic reactions and adverse effects to NSAIDs affecting renal, hepatic, cardiovascular, or gastrointestinal systems (Oladosu et al., 2018). Furthermore, there might be other molecular factors involved in the pain mechanisms of primary dysmenorrhea that are not a target for NSAIDs such as leukotrienes and platelet-activating factor (PAF) (Oladosu et al., 2018; Nigam et al., 1991).

Plant-derived substances and dietary supplements have been studied as alternatives for primary dysmenorrhea; for instance, ginger (Chen et al., 2016). Curcumin is a plant-derived polyphenolic substance, also named *Curcuma longa* and *Curcuma domestica* within the scientific community, naturally found in the turmeric plant, and its roles and medicinal properties have been widely studied. The primary pharmacological agent of the turmeric plant is found in its rhizome; when processed, it can be used as a spice (curry powder, yellow beetroot) (Stanić, 2017).

The potential medicinal and therapeutic properties of curcumin such as its analgesic, antioxidant, and anti-inflammatory properties, causing a reduction in oxidative stress, might pose a potential benefit for some chronic diseases (de Oliveira et al., 2016). Despite previous studies showing poor absorption and fast elimination of the body (Siviero et al., 2015), new approaches seem to improve its bioavailability: by limiting its rapid metabolism, increasing its stability and solubility (Stanić, 2017). Recent nanotechnology-based implementations have been applied for solving the innate properties of curcumin that may restrict its potential benefits and therapeutic applications both in vivo and in vitro studies (Gera et al., 2017).

Curcumin has shown activity against different inflammatory conditions such as asthma, uveitis, inflammatory bowel disease, arthritis, psoriasis, and postoperative inflammation, among others (Aggarwal, 2010) by diminishing circulating pro-inflammatory cytokines and also preventing nitric oxide synthesis (Gera et al., 2017; Aggarwal, 2010). Different studies have shown a positive impact of curcumin on endometriosis (Arablou, T., & Kolahdouz-Mohammadi, R., 2018; Jana et al., 2014). In preclinical studies related to endometriosis, conducted in mice and rats, and in vitro with human cells (Zhang, 2019): an inhibitory effect on oxytocin-induced contractions in the rat's uterus suggests a tocolytic and antispasmodic effect (Thaina et al., 2009). Antioxidant and antinociceptive activities along with inhibition of oxidative stress by the use of curcumin in humans has been reported during exercise and during premenstrual syndrome (PMS) in

women, by regulating the neurotransmitters and biomolecule levels (Gera et al., 2017).

A study used C3 curcuminoid capsule of 500mg to evaluate changes in glutathione S-transferase activity, levels of M1G and PGE2 production in blood and in target tissue; finding a significant decrease in PGE2 production, along with concluding that curcumin is safe at a daily oral dose of 3.6g (Sharma et al., 2004). A phase I trial used oral daily curcumin of a 100, 200, and 400 mg, along with gemcitabine to evaluate NF-kB activity inhibition, cytokine levels, efficacy, and quality of life, this study found no adverse events and concluded that repetitive exposure to high concentrations of curcumin is safe (Kanai et al., 2013).

A significant reduction in the severity of PMS score, was observed in a double-blinded, placebo-controlled, phase II trial, where patients received curcumin capsules orally (100mg every 12h, given 7 days before the beginning of the menstrual bleeding and 3 days after the bleeding onset) to evaluate PMS score in women diagnosed with premenstrual syndrome during their luteal phase, concluding that there is a potential advantage of curcumin in attenuating the severity of PMS symptoms (Khayat et al., 2015).

A phase II, triple-blinded, placebo-controlled trial used rectal suppositories of 350 mg of curcumin extract plus 80 mg of calendula extract, to evaluate NIH-Chronic Prostatitis Symptom Index Score (NIH-CPSI), peak flow and VAS score in patients with chronic prostatitis or chronic pelvic pain syndrome type III; concluding a clinical efficacy of curcumin, based on the improvement of NIH-CPSI, patients' VAS score and a decrease in inflammatory cytokines (Morgia et al., 2017).

Although curcumin has shown many non-specific effects in many trials, it is by the association with excessive macrophage activation, where researchers have seen a specific cumulative effect made by curcumin on inflammatory conditions. As a consequence of the induction of the Glucocorticoid-induced Leucine Zipper (GILZ) protein, the inhibition of the corresponding subsequent pathway is launched, thus contributing with the anti-inflammatory effect (Hoppstädter et al., 2016).

In general, as curcumin has shown nociceptive effects as well as specific and non-specific anti-inflammatory effects, it seems to be a potential candidate for treating cramping pain in primary dysmenorrhea. However, there is no previous trial using curcumin for these specific conditions of pain. To fill this gap of knowledge, this trial aims primarily at the evaluation of the effects of curcumin, compared to placebo, on pain under primary dysmenorrhea, in women aged 18 to 35 years, assessed by the visual analogue pain scale (VAS). Secondarily, effects upon the Cox Menstrual Symptom Scale (CMSS), the presence of adverse effects, amount of rescue drug used and the difference between groups over time as well as the interaction between group and time will be evaluated.

MATERIAL AND METHODS

Trial Design

A phase II, single-center, randomized, triple-blinded, placebo-controlled, two-arm parallel-group design with an equal (1:1) allocation of the subjects to two groups (Curcumin and Placebo). This trial was designed according to the SPIRIT statement, to evaluate the superiority of curcumin in pain reduction in women with primary dysmenorrhea over placebo.

Study Setting

The study would be conducted in a single academic hospital located in an urban area from a large city in the United States; for which three gynecologists would be responsible for gathering the sample population from their patients diagnosed with primary dysmenorrhea, that meet the inclusion and exclusion criteria.

Run-in Phase:

- It is a passive run-in period on which curcumin won't be administered; it is strictly observational.
- To show the patients' baseline behavior, making it easier to learn about side effects truly caused by the use of curcumin.
- To show the number of pills (NSAIDs) and the number of times patients seek medication aid for reducing the pain (rescue drug).
- A questionnaire will be administered to the patients with closed-ended questions to be filled daily regarding the symptoms during their menses, baseline VAS and CMSS pain scores, along with the amount, and the type of medication used.
- Duration: One menstrual cycle - no washout period is required since no intervention would be administered to patients.

Randomization

An Interactive Web Response System (IWRS) will be used to randomize patients and distribute the study drug. During the site initiation visit, study personnel will be trained in the use of the IWRS. The computer system

will generate a patient number when the pharmacist enters the patient's information into the system. The IWRS will track patient eligibility, enroll the patient into one of the cohorts, and distribute drugs to the study site. The system will use blocked randomization (blocks of 4 and 6), stratifying by age groups (18-25 and 26-35), enrolling patients on a 1:1 basis into the two cohorts.

Randomization, drug dispensing, and drug discontinuation will be accomplished by the system. Authorized site personnel must sign in to the IWRS for randomization, study drug assignment, and treatment discontinuation. Using IWRS, an allocation is only available at the time the patient is enrolled, eliminating concerns about concealment prior to assignment and the possibility that the assignment could be changed. This activity would be physically separated from the screening activities done by the study coordinator, effectively blinding them from the cohort assignment.

Blinding

The study will be triple-blinded. Based on the nature of the intervention, participants, physicians (health care provider / investigators), and statisticians shall be blinded to the treatment allocation. In order to assess the masking of the participants, pills (placebo and intervention of curcumin) would be made in similarity in appearance (size, color, and shape), flavor to mask any distinctive taste and with a similar scent.

Both assessments for blinding and pre-trial tests for blinding are covered by IWRS; unblinding of all participants in the trial will be made after the clinical study report is published.

Emergency Unblinding

If it is medically imperative to know what intervention the subject is receiving, pills should be temporarily discontinued if in the opinion of the investigator continuing can negatively affect the outcome of the subject's treatment, as well as if the subject experiences a serious adverse event (which necessitates informing the FDA as soon as possible). The reason for breaking the blinding should be clearly documented by the investigator in the subject's source documentation. IWRS vendors will provide a 24-hour emergency number.

Eligibility Criteria

Inclusion Criteria

- Women aged 18 to 35 years, willing to participate and to comply with all aspects of study protocol.
- Last six months with normal menstrual cycle (Stanić, 2017; de Oliveira et al., 2016).
- Primary dysmenorrhea diagnosed according to the Primary Dysmenorrhea Consensus Guidelines, by a specialized Gynecologist (Burnett, M., & Lemyre, M., 2017).
- Menstrual pain score of ≥ 45 mm on the VAS Pain Scale (Moderate pain, Jensen et al., 2003), measured at run-in phase.
- No routine use of pharmacological or non-pharmacological analgesics.
- Provide written voluntary informed consent.

Exclusion Criteria

- Secondary Dysmenorrhea confirmed by a gynecological ultrasound examination.
- Serious contraindications that could interfere with an adequate assessment of pain (such as progressive central nervous disorder).
- Diagnosed diabetes (all types) and/or Hypertension.
- Diagnosed psychiatric disorders (schizophrenia, epilepsy, alcohol abuse, anorexia, etc.) or recent use of antidepressants in the previous two weeks.
- Pregnancy or intent to be pregnant during the trial period.
- Use of hormonal contraceptives or intrauterine device during the study or at least 2 months before the study.
- Enrolled in other investigational drug studies in the last 6 months.
- Known gastrointestinal conditions that could interfere with the swallowing or the oral absorption or tolerance of study drug.
- Heavy smoker (more than 25 cigarettes/day).
- Alcohol use greater than three units per day.
- Use of pain medications (e.g. NSAIDs) within 7 days of pain testing.
- Previous intake of curcumin as a supplement.

Recruitment

A targeted approach will be used to recruit participants for this trial: recruiting from clinics in the city of the study setting that would be asked for referrals of patients who meet the inclusion criteria, along with patients that assist the clinical center where the trial would be conducted. Finally, posters will be placed in common areas of hospitals and health centers.

Adherence

In order to increase adherence, only four visits will be required after randomization.

The following points must be explained during the first visit to each participant:

- Instructions on the daily dose of capsules, correct storage (15 to 25˚C) and emphasis on using them after a meal.
- Instruct patients to return the bottles used to dispense the drug with any leftovers.
- Patients must complete and bring to each visit a dysmenorrhea diary provided by the investigators, which will include all drugs taken, VAS for pain and CMSS scale in each day during menstrual cycle.
- In case of forgetting to take the medication, they should immediately take the capsule, keeping a minimum interval of 2 hours between consecutive intakes.
- Explain the importance of calling the study investigators in case of any problems (24-hour direct telephone available).

Timeline

The schedule and procedures of this protocol are presented in Figure 1.

Interventions

Eligible patients will be randomized in a 1:1 ratio to the curcumin and placebo arms, receiving either a white capsule of curcumin (dose 500 mg) or placebo every 12 hours, beginning 7 days before the expected start of the menses, and continuing for 2 days after menses begins, for three successive menstrual cycles out of four cycles. Full written guidance on intervention will be provided, along with a numbered blister pack of rescue drugs to each participant, instructed to be used if necessary in case of severe pain. They should keep records of usage in the diary provided and return the blisters with any remaining pills by the end of the study.

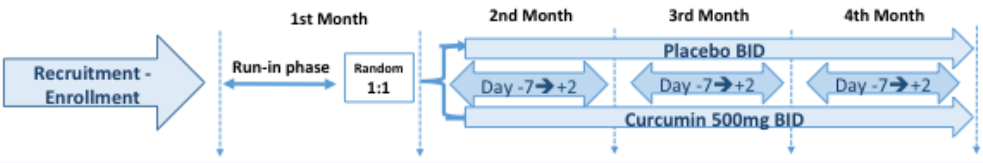
Modification/discontinuation:

- Medication would be discontinued if there are any signs of allergic reactions.
- Gastrointestinal upset: curcumin had shown some minor gastrointestinal symptoms like nausea, vomit, diarrhea.
- Pregnancy: if suspected, intervention must be discontinued.

Outcomes

Primary outcome

- Visual Analogue Scale (VAS) pain: continuous scale from 0-100mm, as difference between groups after 3 consecutive cycles, based on highest score from the first 2 days of menses, collected from the diary questionnaire provided by the investigation team.



Description	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4
Menstrual cycle		Cycle 1	Cycle 2	Cycle 3	Cycle 4
Informed consent form	X				
Medical History	X				
Comorbidities	X	X			
Inclusion/Exclusion criteria	X	X			
Physical Examination	X	X			
Baseline		X			
Randomization		X			
Dysmenorrhea Diary	X	X	X	X	X
Gynecological Abdominal US	X				
VAS for pain	X	X	X	X	X
CMSS	X	X	X	X	X
Urine Pregnancy test	X				X
Report use NSAIDs (amount)	X	X	X	X	X
Drug dispensing		X	X	X	
Adverse events			X	X	X

BID: twice daily; US: ultrasound; VAS: Visual Analogue Scale, ; CMSS: Cox Menstrual Symptom Scale; NSAIDs: non-steroidal anti-inflammatory drugs (Rescue drugs)

Figure 1: Study design, schedule, and trial-related procedures.

Secondary outcomes:

- Side effects of curcumin: reported symptoms that vary from baseline systemic manifestations of dysmenorrhea observed during run-in phase, will be asked for, in every visit and also monitored in the diary provided.
- Cox Menstrual Symptom Scale (CMSS): systemic symptoms median change from baseline after 3 consecutive cycles, measured on the run-in phase, and collected in every visit as reported from the diary.
- Amount (number of pills) of rescue drug required for a mean change from baseline and final value, reported by subjects in the diary.
- Assess difference between groups and change in pain score over time; as well as interaction between group and time.

Data Management

Trial will use a Data Coordination Center (DCC) located at the main site. DCC will be involved starting from the draft of the data management plan, on regular reviews and update up to trial closure. To protect the confidentiality of each subject, numbers will be assigned to each file for identification of the participants. All data will be entered electronically. If data is printed, this would be kept on file and stored in a secure place accessible only to study team members.

A password system will be implemented to ensure secure entries by team members; these passwords would be renewed on each access to the study data. A log sheet would be kept updated, tracking every entry to the system.

Data will be kept in storage for a period of 10 years, after completion of the trial. It is strictly prohibited to use the data archived for any unauthorized purpose or any other research. We will use the System architecture for Clinical Trial Management System, with the Epi info (https://www.cdc.gov/epiinfo/index.html). An interim analysis will not be performed.

Sample Size Calculation

Using a hypothetical population mean of 6 (moderate pain) for the control group from the sample size calculation study, based on observed results from published articles, and considering a SD of 3.0 (large variation - as for a SD of 2.7 reported in literature), with a power of 80%, a total sample size of 90 patients (45 in each group) is required to detect a 30% difference in VAS score using an unpaired t-test with a 0.05 two-sided significance level (Ho:m2=m1 vs Ha: m2! = m1). Allowing for 20% loss to follow up; what means a total of 108 participants (54 per group).

Statistical Analysis for primary and secondary outcomes

VAS pain scale will be used as a continuous variable, with readings from 0-100 mm. Shapiro-Wilk test would be used to assess normality of the data, along with visual comparison with a histogram, and assuming normal distribution of the variable, an unpaired t-test will be used for the analysis of primary outcome (Dexter; Chestnut, 1995), for secondary analyses of the primary outcome, we will perform a paired T-test between baseline VAS pain score and score from the third month, along with an unpaired t-test for the mean difference between groups. If data is not normally distributed, Mann-Whitney test for unpaired test and Wilcoxon signed-rank test for paired test will be applied instead. Secondary outcomes will be analyzed between groups (curcumin versus placebo group) as follows: chi-square or Fisher's exact test will be applied for categorical variables (side effects) along with unpaired t-test for the continuous variable (CMSS and amount used of rescue drug). To assess differences between groups and change in pain score over time, as well as interaction between group and time as exploratory secondary outcome, Two-way ANOVA will be applied.

For all the tests an alpha of 0.05 (2-sided) would be reported to four decimal places. STATA 16 version will be used to conduct analyses. Descriptive statistics will be used to outline the demographic and baseline characteristics, along with the presented side effects that could be listed.

Missing Data

Anticipating missing data, a predictive number for missed observations was included in sample calculation. If missing data rate is higher than 5% complex methods shall be used, specifically based on imputation models.

Considering this study would be randomized and following an Intention-to-Treat as for a non-adherence analysis; multiple imputation will be an adequate choice, including requirements such as: covariates used for the estimation, the number of imputations to be at least the percentage of missing data and to have separate imputation of the intervention and control group. Linear or logistic regression would be performed for the analysis of imputed dataset of continuous and binary variables, respectively. After running all analysis,

sensitivity analysis would be done to examine robustness and accuracy of conclusions.

DISCUSSION

The need for a trial on curcumin and dysmenorrhea arises from clinical evidence that curcumin has shown analgesic and antiinflammatory effects, and therefore it could reduce severity of primary dysmenorrhea and its symptoms, since the physiopathology of this disease is related to those mechanisms (pain and inflammation). This study pools information provided from previously published trials on curcumin, including both Phase I and II trials, that have concluded that the compound is well tolerated, has few mild side effects (gastrointestinal in its majority), shows less side effects on patients than NSAIDs, and exhibiting evidence of efficiency for conditions that involve pain, being the reason why we aim to see an effect of at least 30% reduction in the third cycle, based on potential cumulative effect of curcumin in comparison to placebo.

As for limitations, we consider generalizability of the results could be restricted, since the study would be done in a single center and because it is a phase II, which implies a small sample size. In addition. it can be further affected since patients are allowed to use a rescue drug when the pain becomes unbearable with only the study intervention. Lastly, the application of the VAS pain scale and the CMSS, might present some subjectivity from the participants, because not every subject would have the same method to grade pain level.

Based on previous research, curcumin is considered a good, safe for consumption and affordable candidate for acute-cyclic pain and disabling conditions such as primary dysmenorrhea, turning it to a possible choice among women with allergies or that do not respond to NSAIDs as pain relief aid, increasing options for women to choose the treatment that best fits them.

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Conflict of interests

The authors declare no conflict of interests.

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