Comparison Between 200 µg and 800 µg of Misoprostol for Cervical Ripening Prior to Operative Hysteroscopy: A Study Protocol for A Randomized Controlled Trial.

Maria da Conceição Farias Souto Maior (conceicaosoutomaior@gmail.com)
Centro Universitário Maurício de Nassau - UNINASSAU https://orcid.org/0000-0001-9621-7922
Aurélio Antônio Ribeiro Costa
Instituto de Medicina Integral Professor Fernando Figueira
Alex Sandro Rolland Souza
Instituto de Medicina Integral Professor Fernando Figueira

Study protocol

Keywords: operative hysteroscopy, misoprostol, randomized clinical trial, cervical ripening, cervical width

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Title

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Names protocol contributors

Maria da Conceição Farias Souto Maior (MM)
E-mail: conceicaosoutomaior@gmail.com
Alex Sandro Rolland Souza (AS)
E-mail: alexrolland@uol.com.br
Aurélio Antônio Ribeiro da Costa (AC)
E-mail: aureliorecife@gmail.com

Corresponding author: MM
Av. Rosa e Silva 2075 ap 901, Tamarineira, Recife, Pernambuco, 52.050-020, Brazil.
Phone number: +55 81 99737-5778
E-mail: conceicaosoutomaior@gmail.com

Abstract

Background: Hysteroscopy, a minimally invasive procedure, has been increasingly used to treat disorders of the cervical canal and uterine cavity. However, difficulties related to the insertion of the hysteroscope through the cervical canal still remain. Although there are reported advantages in reducing cervical resistance with the use of misoprostol for cervical ripening, systematic reviews highlight the need to determine the optimal dose. This study was designed to compare two groups of patients submitted to cervical dilatation prior to operative hysteroscopy and pre-treated with either 200 µg or 800 µg of misoprostol for cervical ripening.

Methods: A randomized, quadruple-blind clinical trial with patients submitted to cervical dilatation prior to operative hysteroscopy at university teaching hospitals in Recife, Pernambuco, Brazil. After the internal review boards of the participating institutes had approved the study protocol, data collection began on November 7, 2019, with expected completion on November 1, 2020. Patients included in the study following the informed consent process are randomly allocated to one of two groups, the first allocated to use 200 µg misoprostol and the second to use an 800-µg dose. In both groups, misoprostol will be administered vaginally 10-12 hours prior to operative hysteroscopy. The groups will be compared in relation to intraoperative and postoperative outcomes based on the following endpoints: baseline cervical dilatation, cervical length, degree of difficulty, duration of cervical dilatation, failure to dilate, adverse events and surgical complications. The chi-square test of association, Fisher's exact test and the Mann-Whitney test will be used to compare the groups, with an alpha error of <5% being considered significant.

Discussion: The findings of this study will contribute towards establishing the optimal misoprostol dose for cervical ripening prior to operative hysteroscopy, ultimately facilitating hysteroscope insertion through the cervical canal. A gap will be filled in the currently available literature, providing future preoperative guidance. The 800-µg dose of misoprostol is expected to reduce resistance in the cervix and shorten the time until achieving cervical dilatation, delivering a less traumatic procedure for the patient. Therefore, the study is relevant for surgeons in this field, for the scientific community and, particularly, for patients.

Trial registration: Clinical Trials Register: NCT04152317. Registered on November 5, 2019. URL https://clinicaltrials.gov/ct2/show/study/NCT04152317.

Keywords

operative hysteroscopy; misoprostol; randomized clinical trial; cervical ripening; cervical width.

Administrative information

Title {1}	Comparison between 200 µg and 800 µg of misoprostol for cervical ripening prior to operative hysteroscopy: a study protocol for a randomized controlled trial.
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Author details {5a}	MM [conceicaosoutomaior@gmail.com], AC [aureliorecife@gmail.com], AS [alexrolland@uol.com.br] MM, AC and AS conceived of the study and initiated the study design. AS and AC provided statistical expertise in clinical trial design and will conduct the statistical analysis. The first version of this protocol was drafted by MM and AS. AC revised the final complete version of the protocol. MM will help with implementation. All authors have made substantive intellectual contributions to the manuscript and read and approved its final version
Name and contact information for the trial sponsor {5b}	MM Address: Av. Rosa e Silva 2075 ap 901, Tamarineira, Recife, Pernambuco, 52.050-020, Brazil. Phone number: +55 81 99737-5778 Email: conceicaosoutomaior@gmail.com

Role of sponsor {5c}	In this trial the principal investigator is a “sponsor-investigator” who assumes both sponsor and investigator roles.

Introduction

Background and rationale {6a}

Hysteroscopy has revolutionized the treatment of many benign uterine diseases; nevertheless, as with any other type of surgical procedure, there can be complications (1). The difficulties most commonly reported are those related to inserting the hysteroscope through the cervical canal, particularly when cervical dilatation is required to allow the insertion of larger caliber sheaths. Up to 50% of complications at operative hysteroscopy occur at this moment (2). Cervical tears, the creation of a false passage, uterine perforation, bleeding and difficulty when inserting the hysteroscope through the cervical canal are the most common complications encountered during the dilatation procedure (3). This step is extremely important, bearing in mind that difficulty in dilating the cervix may result in the surgeon having to abandon the procedure.

Adequate cervical ripening can reduce the rate of complications associated with the difficulties encountered when inserting the hysteroscope (1,3). The methods used for cervical ripening are based on osmotic dilators (laminaria) and natural and synthetic prostaglandins. Misoprostol, a synthetic prostaglandin, has been shown to induce fewer surgical complications when compared to placebo or to other methods (4–6).

Prostaglandins exert different effects on the cervix, acting basically on the extracellular matrix, leading to dissolution of the collagen fibers and to an increase in hyaluronic acid and the water content of the cervix. In addition, they relax the smooth muscles of the cervix and increase the concentration of intracellular calcium, promoting a gentle uterine contraction. All these mechanisms allow a progressive reduction in the resistance of the cervix, greatly facilitating cervical dilatation together with a gentle initial increase in uterine activity (7).

The effectiveness of misoprostol administered prior to hysteroscopy for cervical ripening is well documented in systematic reviews and meta-analysis. A 2015 Cochrane systematic review evaluated whether preoperative ripening of the cervix would facilitate cervical dilatation and reduce complications during operative hysteroscopy (8). Misoprostol was compared with no treatment, placebo, dinoprostone (a natural prostaglandin) and laminaria (osmotic dilators). Nineteen randomized clinical trials (RCT) were included, involving a total of 1,870 participants. Misoprostol was found to be more effective for cervical dilatation than placebo or no intervention, with fewer women requiring mechanical dilatation (OR: 0.08; 95%CI: 0.04-0.16, five RCT; 441 participants). In a population in which 80% of women undergoing hysteroscopy with no pre-treatment would require mechanical dilatation, the use of misoprostol would reduce that need to between 14% and 39%. Misoprostol was also associated with fewer intraoperative complications (OR: 0.37; 95%CI: 0.18-0.77; twelve RCT; 901 participants). In a population in which 3% of women undergoing hysteroscopy with no pre-treatment would experience complications, the use of misoprostol would reduce this proportion to 2% or less. When the complications were evaluated individually, the group that used misoprostol had a lower rate of

cervical tear (OR: 0.25; 95%CI: 0.11-0.57; nine RCT; 669 participants) and fewer cases of false passage creation (OR: 0.34; 95%CI: 0.12-0.97; seven RCT; 560 participants). No difference was found between the groups when the rates of uterine perforation (OR: 0.42; 95%CI: 0.13-1.38; seven RCT; 455 participants) and uterine bleeding (OR: 0.51; 95%CI: 0.10-2.49; four RCT; 340 participants) were evaluated. Some adverse events such as abdominal pain, vaginal bleeding and an increase in body temperature were more common in the group that used misoprostol (8).

The need for cervical dilatation was less and the time required to achieve dilatation was shorter, as corroborated by other systematic reviews conducted in 2016 (9,10). One of those reviews, involving 25 RCT with a total of 2,203 patients, concluded that the use of misoprostol reduces the need for cervical dilatation compared to placebo or no treatment at all. Use of the medication resulted in greater baseline cervical dilatation and a lower rate of complications at hysteroscopy, with moderate or mild side effects (10). Systematic reviews have also shown a lower rate of complications such as cervical tear and the creation of a false passage at hysteroscopy (8,10,11).

Nevertheless, there are several issues in the clinical trials selected, as shown in the Cochrane systematic review, in which biases failed to be found in only one of the studies included in the review (8). The sets of trials included in the various systematic reviews were considerably heterogenous. Sometimes, the same review combines studies involving diagnostic hysteroscopy with cases of operative hysteroscopy, in which the instrument used is generally of a larger caliber. Likewise, studies were included that involved different administration routes and dosages. Nevertheless, the feature that differed most refers to the dose of the medication. Trials are included in which the dose used ranged from 100 µg to 1,000 µg (12–14).

The most recent systematic reviews highlight the need to determine the optimal dose of misoprostol (8,10). A very recent clinical trial evaluating the best route of administration recommended further investigation with respect to various aspects, including dose (15). Therefore, the objective of the present study is to contribute towards filling this gap in currently available information.

Objectives {7}

The objective of this study is to compare intraoperative and postoperative outcomes in patients submitted to cervical dilatation using misoprostol at a dose of 200 µg or 800 µg for cervical ripening prior to operative hysteroscopy. The endpoints to be evaluated are cervical findings (baseline cervical dilatation, ease of dilatation, total time required for cervical dilatation up to 9 mm, length of the cervix and failure to achieve dilatation); type and frequency of adverse events following misoprostol use; type and frequency of intraoperative complications (uterine perforation, creation of a false passage, cervical tear, post-dilatation bleeding) and patient satisfaction level.

Trial design {8}

This randomized, controlled and quadruple-blind clinical trial is an exploratory study consisting of two parallel

groups, with the primary endpoints being intraoperative and postoperative outcomes resulting from the use of misoprostol administered vaginally at doses of 200 µg or 800 µg for cervical ripening prior to operative hysteroscopy. Simple randomization was performed according to previously prepared, computer-generated, random number tables with a 1:1 allocation.

Methods: Participants, interventions and outcomes

Study setting {9}

The study is being conducted at four public university teaching hospitals in Recife, Pernambuco, in northeastern Brazil, all of which are accredited by the Brazilian Ministries of Health and Education: the *Instituto de Medicina Integral Prof. Fernando Figueira* (IMIP), the *Hospital Agamenon Magalhães* (HAM), the *Hospital Barão de Lucena* (HBL) and the *Centro Integrado de Saúde Amaury de Medeiros* (CISAM). These institutes were selected in view of the fact that they routinely admit patients to hospital on the eve of the surgical procedure, allowing the medication to be administered at the established schedule and the patient to be monitored.

To reduce the possibility of bias, specialists with similar levels of experience working in the gynecological endoscopy teams in the participating institutes will perform all the hysteroscopy procedures.

Eligibility criteria {10}

Patients for whom operative hysteroscopy was indicated are considered potential candidates for inclusion in the study. Patients under 18 years of age and those for whom the use of prostaglandins is contraindicated (patients with asthma, glaucoma, kidney failure, severe heart disease or allergy to the medication) are excluded from the study. Severe pelvic organ prolapse and virginity, which would prevent the medication from being administered vaginally, and situations that prevent hysteroscopy from being performed, including significant uterine bleeding, diagnosed or suspected pregnancy and genital infections such as bacterial vaginosis and cervicitis, are also considered exclusion criteria. Factors that can affect baseline cervical dilatation also constitute exclusion criteria and include: a history of cervical insufficiency, major surgery to the cervix (conization or trachelectomy), the presence of uterine fibroids or polyps extruding from the external cervical ostium, and the presence of structural anomalies of the cervix reported on ultrasonography and/or diagnostic hysteroscopy. Other exclusion criteria consist of the use of systemic or vaginal hormone replacement therapy and recent use of gonadotropin-releasing hormone analogues (GnRHa).

Who will take informed consent? {26a}

The principal investigator will verbally describe the trial to potential participants who will then be given easily understandable written information. Based on that, the potential participants will then have the opportunity to discuss the trial with the investigator and ask questions.

All the participants will be duly informed with respect to the study objectives and methodology. The right of any

candidate to refuse to participate in the study will be made clear. All the women will be informed with respect to the expected risks and benefits. They will also be told that their participation will not involve any additional costs and that they will be entitled to compensation in case of harm. They have the right to ask questions at any time and their right of access to the study results is guaranteed.

After confirming that the women understand the nature of the study and that their participation is voluntary, the investigator will then obtain signed written consent from those willing to take part in the study. A woman will only be included if she agrees to participate and signs an informed consent form. Information sheets and consent forms will be provided for all the women involved in the trial.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Not applicable: no biological specimens will be collected from participants.

Interventions

Explanation for the choice of comparators {6b}

Most of the publications currently available deal with the administration of misoprostol prior to operative hysteroscopy at a dose of 200 µg or 400 µg. However, knowing that cervical consistency is firmer in non-pregnant women (16) we believe that increasing the dose may result in less resistance of the cervix, facilitating dilatation with Hegar dilators and ultimately benefiting the patient by making insertion of the hysteroscope less traumatic.

Use of misoprostol in obstetrics at doses many times higher than those proposed here, even when the dose is repeated over a 24-hour period, reaching a total of up to 2,400 µg/day (17) shows how safe this drug is and that the proposal to evaluate the response of the cervix after application of 800 µg of the drug is ethically acceptable.

Of the clinical trials included in the systematic reviews, only two studies used a dose of 800 µg prior to operative hysteroscopy. In the first, published in 2004, four groups of 12 women were randomly assigned to receive either placebo or vaginal misoprostol at the doses of 200, 400 or 800 µg four hours before the surgical procedure. The authors concluded that none of the three different doses reduced the need for cervical dilatation or improved the ease with which hysteroscopic surgery was performed, and that preoperative pain increased (13). However, the small sample size and the short time between application of the drug and the time of surgery could explain these results.

The other publication, conducted with 204 patients, evaluated a misoprostol dose of 800 µg divided into two doses of 400 µg that were administered 24 and 12 hours prior to the procedure. That study concluded that misoprostol performed better for cervical dilatation in premenopausal and postmenopausal women when

compared to placebo or to pre-treatment with a GnRHa. Adverse effects were more common in the misoprostol group, but in general, they were tolerable and did not contraindicate use of the drug (5).

Based on this, we hypothesized that the administration of a single 800-µg dose could result in the same benefits, with the added advantage of the regimen being more convenient for the patient. The present randomized clinical trial protocol was then elaborated, in which the degree of cervical ripening will be compared between the use of misoprostol at the dose of 200 µg and at the dose of 800 µg.

Intervention description {11a}

The pharmaceutical company *Hebron Indústria Farmacêutica* (Pfizer, Recife, Pernambuco, Brazil) produced the 200-µg misoprostol tablets. Tablets identical in shape, size, color, weight, odor and solubility but without the active ingredient were also ordered from the same pharmaceutical company.

Opaque cardboard boxes, each containing four tablets, were then prepared. Half the boxes contain one 200-µg tablet of misoprostol and three tablets without the active principle, while the remaining boxes contain four 200-µg tablets of misoprostol corresponding to a dose of the medication of 800 µg. The boxes are only to be opened at the moment of administration.

Eligible patients will be randomized in equal proportions to the 200-µg or 800-µg groups and given the medication 10-12 hours prior to the procedure. The four tablets are administered vaginally as a single dose by the principal investigator.

Criteria for discontinuing or modifying allocated interventions {11b}

If the patient refuses to continue in the study in the moments preceding administration of the tablets, she will be discontinued from the study (consent withdrawn).

If significant side effects or unexpected severe reactions are suspected following intravaginal misoprostol application, any residue of the medication will be removed from the patients. This should then be reported as an adverse event and will constitute another criterion for discontinuation from the intervention.

Strategies to improve adherence to interventions {11c}

Since the study medication is administered as a single dose during hospital stay, no issues involving compliance are expected. Nevertheless, if the patient asks any questions between the time of signing the informed consent form and the moment at which the medication is administered, any explanations required to help her reach a decision will be given. If she nevertheless decides to withdraw her consent to participate in the study, her wishes will be respected in accordance with the ethical requirements.

Relevant concomitant care permitted or prohibited during the trial {11d}

To prevent co-intervention bias and promote comparability between the study groups, the protocol lists the relevant concomitant interventions that are forbidden during the study such as the use of systemic or vaginal

hormone replacement therapy, defined as the use of medication for the purpose of treating postmenopausal estrogen deficiency, including, for example, the use of conjugated estrogens, estradiol or promestriene. This type of drug could alter intraoperative outcomes.

Provisions for post-trial care {30}

The accredited hospitals will provide care to any patients who suffer harm from trial participation and will continue to provide routine healthcare to the participants after the trial has been completed.

Outcomes {12}

Primary Outcome Measure:

The primary outcome measure is the degree of cervical dilatation, graded from zero to nine millimeters and measured according to the maximum size of Hegar dilator that can be inserted through the internal ostium without resistance. [Time Frame: during the surgery]. A study that evaluated the mean baseline cervical dilatation at hysteroscopy considered a difference of 1.6% to be statistically significant (14).

Secondary Outcome Measures:

- The time required to dilate the cervix to nine millimeters, defined as the time needed to achieve cervical dilatation up to nine millimeters by inserting Hegar dilators through the internal ostium. [Time Frame: during the surgery]. This measure will provide a good overall comparison between the two treatment arms.
- The degree of ease or difficulty reported by the surgeon while dilating the cervix, evaluated on a scale of 1 to 5 using a Likert-type scale in which a score of 1 reflects extreme difficulty and a score of 5 reflects extreme ease. Results will be described as proportions of cases. [Time Frame: during the surgery].
- The length of the cervix, defined as the distance between the external ostium and the internal ostium, measured in centimeters. [Time Frame: during the surgery].
- Proportion of abandonment of the procedure due to failure to dilate, defined as the impossibility of performing operative hysteroscopy due to difficulty in achieving complete cervical dilation up to nine millimeters. [Time Frame: during the surgery].
- The proportion of intraoperative complications defined as complications related to the degree of difficulty in dilating the cervical canal. These include uterine perforation, the creation of a false passage, cervical tear and post-dilatation bleeding. [Time Frame: during the surgery].
- The proportion of participants reporting adverse events in the 24 hours following randomization. At each evaluation, participants will be questioned with respect to the adverse events they have experienced since the last evaluation moment (using a standard list of known side effects of misoprostol such as nausea, vomiting, diarrhea, fever, chills, or any other complaint resulting from use of the medication). [Time Frame: 24 hours].
- The degree of pain reported by the patient. This is evaluated using a visual analogue scale (VAS) at three different moments: at the time of admission to hospital, prior to surgery (between administration of the medication and initiation of anesthesia) and postoperatively (12 hours after the procedure).

[Time Frame: 24 hours].

- The mean number of participants reporting the different degrees of satisfaction with the medication, evaluated using a Likert-type scale in which scores range from 1 to 5, with 1 reflecting extreme dissatisfaction and 5 meaning that the woman was extremely satisfied with the drug. [Time Frame: 24 hours].

Participant timeline {13}

After the participant has signed the informed consent form, the investigator will complete the hospital admission form, which includes questions on events such as pain, measured using the VAS pain scale, the patient's gynecological and obstetric history, and her personal history of previous pathologies and surgeries. Additional data registered on this form include the results of a complete physical examination, data on why hysteroscopy was indicated, and endometrial echo, as measured in millimeters by ultrasonography.

The drug is administered approximately 10-12 hours before the procedure. Minutes prior to surgery, a preoperative form is completed with data on possible side effects including the intensity of pain, measured using the VAS pain scale.

Shortly after surgery with cervical dilatation, the measurements of the cervix, as well as the time until dilatation and the surgeon's impressions are recorded on the intraoperative form.

Finally, the last patient evaluation takes place around 6-12 hours after surgery. Once again, questions on side effects and the intensity of pain, measured using the VAS pain scale, and information on the degree of satisfaction reported by the patient regarding the use of the medication are recorded on the postoperative form.

	STUDY PERIOD						
	Enrolment	**Allocation**	**Post-allocation**				**Close-out**
TIMEPOINT**	$-t_1$	0	t_1	t_2	t_3	t_4	t_5
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
INTERVENTIONS:							
Hospital Admission Form			X				
Drug administration				X			

Preoperative form					X		
Intraoperative form						X	
Postoperative form							X
ASSESSMENTS:							
Degree of pain			X		X		X
Adverse events					X		X
Length of the cervix						X	
Degree of cervical dilatation						X	
Time to dilate the cervix						X	
Degree of ease or difficulty to dilate						X	
Failure to dilate						X	
Intraoperative complications						X	
Degrees of medication's satisfaction							X

A flowchart will be constructed for the clinical trial in accordance with the guidelines of the Consolidated Standards of Reporting Trials (CONSORT) Statement (18) and will include the overall number of patients referred for operative hysteroscopy during the study period, the number of eligible patients, the number of those invited to participate in the study, the number of women who refused to participate and their reasons for refusing, the number of patients who agreed to participate and the number randomized to receive misoprostol at the two different doses proposed (this information will only be known after the statistical analysis is complete), the total number of patients who were and who were not submitted to the procedure and the reasons, the total number of patients analyzed and those excluded from the analysis, including the reason for this exclusion.

Sample size {14}

Sample size was calculated based on a previous study in which the mean baseline cervical dilatation was determined following use of misoprostol or placebo for cervical ripening prior to operative hysteroscopy (14). A mean difference of 1.6% was found in *premenopausal* women: 4.8% in the misoprostol group compared to 6.4% for the placebo group, with a 95% confidence interval (95%CI 0.5-2.7). No statistically significant difference was found in the groups of *postmenopausal* women.

Calculation was performed using the formula contained in the OpenEpi software program, version 3.01, with the statistical parameters for this calculation including a type I error of 0.05 and a power of 80%. Sample size was thus established as 60 women. To compensate for possible loss to follow-up and post-randomization exclusion, an extra 20% was added to the sample size, making a total of 72 participants. This number was then rounded up to 80 participants. Based on a computer-generated randomization table, 40 women will be allocated to receive prior treatment with misoprostol at a dose of 200 µg and 40 to prior treatment with misoprostol at a dose of 800 µg.

Recruitment {15}

A medical resident in the gynecological endoscopy unit identifies possible candidates for the study on the day preceding their scheduled hysteroscopy and applies a checklist of the inclusion and exclusion criteria, thus determining whether that individual woman is eligible for inclusion in the study. This will result in a convenience sample consisting of patients who fulfill the eligibility criteria and who are receiving care at one of the four participating hospitals between November 7, 2019 and November 1, 2020.

Assignment of interventions: allocation

Sequence generation {16a}

The patients will be randomly assigned either to the 200-µg or to the 800-µg group with a 1:1 allocation in accordance with a computer-generated table for simple randomization generated by the Random Allocation software program.

The investigator responsible for preparing the medication boxes will not participate in the data collection or data analysis. The boxes containing either the 200-µg or the 800-µg dose of misoprostol are identical and an identification number is assigned to each one.

Concealment mechanism {16b}

Each participant is randomized to one of the two study groups, with one of the previously prepared and sealed cardboard boxes being allocated to each one. These boxes contain misoprostol at a dose of 200 µg or 800 µg in accordance with the randomization number. Neither the investigator nor the patient knows what is contained in the box. The boxes will only be opened when the tablets are to be administered.

Therefore, at no time is the investigator or the patient aware of the dose of the medication administered to the participant, neither prior to her signing the informed consent form nor when the tablets are administered. Allocation concealment will be maintained until data collection is complete.

Implementation {16c}

One of the members of the research team who does not participate in the data collection or data analysis was responsible for generating the allocation sequence and for preparing the packaging of the medication. This is the only person who is aware of the contents of each package. This investigator placed four tablets into each cardboard box, with one set of boxes containing one 200-µg tablet and three placebo tablets and the other set of boxes containing four 200-µg tablets corresponding to a total dose of misoprostol of 800 µg. The packages are securely stored in a locked cabinet under the responsibility of the principal investigator for exclusive use in this study.

After application of the inclusion/exclusion criteria by a medical resident at the gynecological endoscopy unit, the principal investigator invites the eligible candidates to participate in the study, verbally explaining the study objectives. The informed consent form, in which the study objectives and the possible consequences of participation are described, is then presented. If the candidate agrees to participate in the study and signs the informed consent form, she is then randomized to one of the two study groups.

The principal investigator also administers the medication 10-12 hours prior to the surgical procedure. The box is opened in the patient's presence and the investigator administers the four tablets found in the box as a single dose by the vaginal route.

Assignment of interventions: Blinding

Who will be blinded {17a}

The same pharmaceutical company manufactured all the tablets, both those containing the medication and those without the active ingredient, taking care to ensure that their characteristics were identical insofar as size, color, shape, weight, smell and solubility are concerned. An investigator, who will not participate in administering the tablets or in the data collection, prepared the packaging and numbering.

The principal investigator, responsible for administering the medication, is unaware of the dose of the medication to be applied, thus guaranteeing concealment. Likewise, the study participant is unaware of the dose she is receiving, thereby ensuring that the patient is also blinded.

If, at the time of the surgical procedure, the surgeon identifies any residue from the medication in the vagina, he/she would be unable to guess the dose used, since it would consist of material from four tablets irrespective of which group the participant belonged to. In all cases, the amount of material found would be equivalent, since all the participants would have received the same number of tablets, thus ensuring that the surgeon is blinded.

For the statistical analysis, the study arms will be referred to as Groups A and B, thus guaranteeing that the statistician is blinded. It is only after the results have been completely evaluated and the study report drafted that the investigator responsible for concealing the randomization procedure will reveal the dose of the medication corresponding to each group. Therefore, the study participants, observers, care providers,

including the surgeon, outcome assessors and the statisticians conducting the data analysis, will all be blinded.

Procedure for unblinding if needed {17b}

Unblinding and discontinuation of the study by ending participant recruitment will take place if severe unexpected adverse events arise that are associated with the medication used and that could be life-threatening or could result in physical or psychiatric damage to patients. Notwithstanding, such events are extremely unlikely, since none has been described in the literature.

Data collection and management

Plans for assessment and collection of outcomes {18a}

The data are being collected using standardized forms, pre-coded for data entry. These instruments have been previously tested and amended as required to meet the specific objectives of this study.

Two members of the research team are responsible for completing the hospital admission form and the postoperative form, with the first ten such forms having been completed by both individuals so as to standardize the recording of the data. Members of the medical team providing care for the patient during surgery complete the forms that deal with the preoperative and intraoperative data. To ensure the quality of the data collection methodology, all the members of the team were previously trained on how to complete the forms appropriately. At that time, each endpoint was clearly defined, and the technique to be used for its evaluation clearly explained, including instructions on how to apply the VAS pain scale and the Likert-type scale. The forms used are attached to this protocol as additional files.

Plans to promote participant retention and complete follow-up {18b}

Since this is a clinical trial conducted to determine the best dose of the medication applied as a single dose, with in-hospital follow-up of approximately 24 hours after the intervention, loss to follow-up in this group of patients is considered highly unlikely. Nevertheless, cases of missing data referring to the surgical procedure could occur if surgery were suspended or postponed. In such cases, data concerning the side effects of the medication and the patient's satisfaction level will still be collected.

Data management {19}

After manual data collection using the questionnaire, the investigators will rigorously review the information collected. The data from the forms will be entered (in blocks of ten) into a database specifically created for the study using Epi-Info, version 3.5.4 for Windows. Double entry of data will be performed, i.e. two different people will perform data entry at two different moments. A printout of the two databases will be obtained for comparison and correction of any possible data entry errors. A definitive database will thus be created, which will then be submitted to data cleaning techniques to ensure consistency, after which copies will then be made. That database will then be used for the statistical analysis. All the forms and the signed consent forms related

to the study will be kept in locked cabinets. Access to the study data will be restricted.

Confidentiality {27}

Data will be anonymized and patient records will remain confidential during the study and after its completion. Only those data inherent to the development of the study will be disclosed at the time of publication. During the informed consent process, this will be made clear to the participants, as well as the fact that any personal data that could identify them will be destroyed at the end of the study, with nothing remaining that could compromise their right to anonymity.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Not applicable: no biological specimens for genetic or molecular analysis will be collected.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

The data will be analyzed using Epi-Info, version 3.5.4. A bivariate analysis will be performed to test the randomization by comparing the characteristics of the patients in the two groups (control variables). Although this is a controlled clinical trial, this important step will control for differences between the groups that could occur even by chance, negatively affecting the results.

Next, an analysis will be performed to test the association between the independent variable (the dose of the medication received prior to hysteroscopy) and the dependent variables (the outcomes). Two by two contingency tables will be constructed for the categorical variables using the chi-square test of association with Yates correction for continuity and Fisher's exact test if required (if one of the expected values is <5).

The Kolmogorov-Smirnov test will be used to test the normality of the numerical variables using the SPSS statistical software program, version 10.0. If the distribution is not normal, the Mann-Whitney non-parametric test will be used to compare the two groups and medians will be used as the measure of central tendency for the variables with these characteristics. The Mann-Whitney test will also be used to assess any differences between the ordinal variables from the VAS pain score. This outcome will be measured at three different evaluation moments and classified as distinct variables such as pain A, pain B and pain C. Some of the numerical variables could be categorized for analysis according to their distribution, taking cut-off points into consideration, such as in the case of the variable "*duration of the dilatation procedure*". Different cut-off points could therefore be tested during the statistical analysis.

In all the steps of the analysis, an alpha error of less than 5% will be considered statistically significant.

Interim analyses {21b}

Not applicable: the sample size is small and the duration of data collection will be short.

Methods for additional analyses (e.g. subgroup analyses) {20b}

Due to the strong biological justification, a subgroup analysis will be performed based on patients' menopausal status. We will test whether the effects of the medication at the different doses differ between the participants as a function of their menopausal status.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Even in the cases in which the participant complains of discomfort following application of the medication, she will be considered part of the group to which she was initially allocated at randomization (intention-to-treat analysis) and will not be excluded from the study.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

The protocol will be published in indexed journals and the corresponding author's e-mail address will be made available. The corresponding author will be responsible for answering questions from the scientific community. The data will also be updated periodically at ClinicalTrials.gov.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

Predicting the possibility of operational issues such as technical or clinical limitations, it was decided not to perform the study in a single research center but to make it multi-centered. Based on the fact that no interim analysis will be conducted due to the sample size and the short data collection period, the creation of a coordinating center or trial steering committee was deemed unnecessary.

Composition of the data monitoring committee, its role and reporting structure {21a}

A data monitoring committee is deemed unnecessary, since the predicted duration of this clinical trial is short. Furthermore, the administration of the medication is considered only mildly invasive and well tolerated by patients, and the possible side effects are considered mild to moderate and easily resolved, bearing in mind that the medication has been well known to physicians for decades.

Adverse event reporting and harms {22}

In this study, an adverse event is defined as any untoward medical occurrence in a subject without regard to

the possibility of a causal relationship. Data on adverse events will be collected after the subject has provided consent and enrolled in the study. If the participant experiences an adverse event after the informed consent document is signed (entry), but the patient has not yet begun to receive the study intervention, the event will be reported as being unrelated to the study drug. All adverse events occurring after entry into the study and until hospital discharge will be recorded.

Although generally well tolerated, the following adverse effects of misoprostol treatment have been described: diarrhea, abdominal pain, nausea, vomiting, flatulence, abnormal vaginal bleeding, skin rash, headache, shivering and hyperthermia. Their occurrence during the present trial may, however, be unlikely given that the treatment is administered as a single-dose. Study personnel will use the VAS to monitor pain in the patients (19).

Frequency and plans for auditing trial conduct {23}

A periodic independent review of the principal evaluation processes and documents is being conducted based on monthly reports in which the progress in data collection is documented. The actual progress made in the study compared to what was predicted in the chronogram and the possible difficulties in maintaining the schedule are also checked. The processes associated with enrollment, consent, eligibility and the allocation of the participants to the groups are also reviewed, and the policies for safeguarding patients, including reports of harm and integrity, as well as the precision and punctuality of data collection are monitored. The study is being conducted with resources provided by the investigators involved in it and an auditor is monitoring this aspect. At the time of data analysis, an audit will also be performed.

Professor José Roberto S. Junior, coordinator of the *stricto sensu* postgraduate program at the *Instituto de Medicina Integral Prof. Fernando Figueira*, Recife, Pernambuco, Brazil (institutional e-mail: roberto.junior@imip.org.br; telephone +55 81 21224122) will perform this procedure completely independently from the study investigators. He is not part of the research team involved in this study.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Any modifications to the protocol that may impact on how the study is conducted or affect potential benefit to the patient or patient safety, including changes to the study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects, will require a formal amendment to the protocol. Such amendments will have to be approved by the internal review boards and Clinical Trial Registration System prior to implementation.

Dissemination plans {31a}

The trial findings will be made public through presentations at national and international conferences and publications in peer-reviewed journals. Authorship will be defined according to the criteria for authorship

developed by the International Committee of Medical Journal Editors (ICMJE). Results will also be shared with all the trial participants. Every attempt will be made to reduce to an absolute minimum the interval between the completion of data collection and the release of the study results. We expect to take about 3 to 4 months to compile the final results as a paper to be published in an appropriate peer-reviewed journal. The study results will be released to the participating physicians, referring physicians, patients and to the general medical community. To guarantee transparency and reproducibility, the complete study protocol containing all the relevant details will be published in an open access journal.

Discussion

A considerable percentage of the complications at operative hysteroscopy are related to problems involving the insertion of the hysteroscope through the cervix. At times the procedure proves impossible, thus justifying its suspension. Adequate cervical ripening in women with an indication for hysteroscopy could minimize complications, making the technique safer and more effective.

Data in the literature have shown the ability of misoprostol to promote changes to the cervix that make manipulation easier, particularly in pregnant women. In gynecology, systematic reviews have concluded that results are positive; however, they also agree that further clarification is required to determine the optimal dose.

The present study is relevant given that the findings will potentially improve the ease with which surgeons will be able to insert the hysteroscope into the cervix. The results will also be of interest to the scientific community, since they will contribute towards clarifying the optimal dose for cervical ripening prior to operative hysteroscopy, information that is currently lacking, thus providing a basis for future preoperative guidance. The patient will be the principal beneficiary of a safer and less traumatic procedure that will involve a lower rate of intraoperative complications.

In view of the increasing use of misoprostol in gynecology, the importance of adequate cervical ripening aimed at reducing trauma during the surgical procedure and the lack of clarity regarding the optimal dose of misoprostol, this project was drawn up to compare the degree of cervical ripening with the use of misoprostol at the doses of 200 µg and 800 µg in a randomized clinical trial.

Trial status

Protocol version number 1, June 8, 2020.
Date recruitment began: November 7, 2019.
Approximate date when recruitment will be completed: November 1, 2020

Initially, data collection was expected to terminate at the end of June 2020; however, with the onset of the COVID-19 pandemic, this schedule has had to be altered, since elective hysteroscopy procedures have been

temporarily cancelled following the recommendations for hysteroscopic procedures during the COVID-19 Pandemic (20). The current schedule is to finish the data collection is November 1, 2020.

Abbreviations

CISAM	*Centro Integrado de Saúde Amaury de Medeiros*
GnRHa	Gonadotropin-releasing hormone analogues
HAM	*Hospital Agamenon Magalhães*
HBL	*Hospital Barão de Lucena*
IMIP	*Instituto de Medicina Integral Prof. Fernando Figueira*
VAS	Visual analogue scale

Declarations

Acknowledgements

The authors would like to thank the local surgeons and care providers who will be responsible for the procedures and for providing care to the patients.

Authors' contributions {31b}

MM, AC and AS conceived and designed the study. AS and AC provided statistical expertise regarding the study design and will conduct the statistical analysis. The first version of this protocol was drafted by MM and AS. AC revised the final complete version of the protocol and MM has collaborated in implementing the protocol. All authors have made substantive intellectual contributions to the protocol and read and approved this final version.

Funding {4}

Since this study received no support, either of a financial or non-financial nature, no role is played by any third parties in the study design, in the procedures of collection, analysis, or interpretation of the data, or in the decision to submit results.

The misoprostol and placebo tablets were manufactured by Hebron (Pfizer, Recife, Pernambuco, Brazil) and purchased for use in the study. The manufacturers of misoprostol play no role whatsoever in the design, management, analysis or reporting of the study.

Availability of data and materials {29}

The datasets to be used and/or analyzed during this clinical trial will be made publicly available from the corresponding author upon reasonable request.

Ethics approval and consent to participate {24}

The present study will comply with the requirements for research studies involving human beings determined by the Brazilian National Health Council under Resolution 466/2012. The project has already been registered on the *Plataforma Brasil* and was submitted for analysis to the internal review boards of IMIP, HAM and CISAM/UPE. Data collection was only initiated after approval by the respective internal review boards. The *Hospital Barão de Lucena* does not have its own internal review board and agreed to accept the approval decision made by the other internal review boards.

Board Name: IMIP's Ethics Committee on Human Research
- CAAE: 04261318.1.0000.5201
- Approval Number: 3.146.099
- Approval Date: February 14, 2019

Board Name: HAM's Ethics Committee on Human Research
- CAAE: 04261318.1.3002.5197
- Approval Number: 3.204.655
- Approval Date: March 18, 2019

Board Name: CISAM/UPE's Ethics Committee on Human Research
- CAAE: 04261318.1.3001.5191
- Approval Number: 3.298.706
- Approval Date: May 02, 2019

Informed consent will be obtained from all study participants.

Consent for publication {32}

In the informed consent form, there is a specific section in which the participant authorizes the disclosure in scientific events and publication in the literature of all the information provided by her, except for personal data.

Competing interests {28}

The authors declare that they have no competing interests. There is no financial interest in any product or service related to the research and there is no support in any way by a company or organization.

Authors' information

1. MM

Universidade Católica de Pernambuco (UNICAP), Recife, PE, Brazil;

Universidade Maurício de Nassau (UNINASSAU), Recife, PE, Brazil;

Hospital Agamenon Magalhães (HAM), Recife, PE, Brazil.

2. AC

Universidade de Federal de Pernambuco (UFPE), Recife, PE, Brazil;

Faculdade Pernambucana de Saúde (FPS), Recife, PE, Brazil;

Instituto de Medicina Integral Prof. Fernando Figueira (IMIP), Recife, PE, Brazil.

3. AS

Universidade Federal de Pernambuco (UFPE), Recife, PE, Brazil;

Universidade Católica de Pernambuco (UNICAP), Recife, PE, Brazil;

Instituto de Medicina Integral Prof. Fernando Figueira, Recife (IMIP), PE, Brazil.

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