Universidade Federal do Rio Grande do Sul

Faculdade de Medicina

Departamento e Serviço de Ginecologia e Obstetrícia

Research Project

Comparison Between 400 µg or 200 µg of Misoprostol for Cervical Dilatation in 1st Trimester Miscarriage - A Clinical Trial

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Research Group and setting

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The authorship of the work will be based on the criteria established by the **International Committee of Medical Journal Editors**. All persons designated as authors must be qualified for, and all those who are qualified, must be listed. Each author must have participated sufficiently in the work to have public responsibility for appropriate portions of the content. One or more authors must have responsibility for the integrity of the work as a whole, from the beginning to the publication of the article. Authorship credits should be based only on:

1. substantial contribution to the conception and design, the acquisition of data, or

the analysis and interpretation of the data;
2. writing of the article or its critical review for important intellectual content;
3. final approval of the version to be published.
All conditions 1, 2, and 3 must be met. The acquisition of funds, data collection, or general supervision of the research group, by themselves, does not justify authorship.
Authors must describe what they contributed, and editors must publish such information. All others who contributed to the work who are not authors should be named in the acknowledgments, and what they did should be written.

Original place of the study:

FAMED

Rua Ramiro Barcelos, 2300; 4º floor, Department of Gynecology and Obstetrics

The place to be carried out the project:

HCPA

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Introduction

Miscarriage is defined by the World Health Organization as the interruption of the pregnancy up to 20-23 weeks, or the products of pregnancy weighing less than 500 grams (1). Nearly 15% of known pregnancies end in miscarriage, especially in the first 12 weeks. Estimates indicate that 68000 women die worldwide each year, as a result of unsafe abortions. Abortions are the major cause of maternal death, particularly in Latin America and the Caribbean. In cases of retained and incomplete abortions, uterine emptying is recommended. In the first trimester of pregnancy, either pharmacological or surgical procedure is accepted according to international guidelines.

Pharmacological treatment for uterine evacuation includes the administration of mifepristone and misoprostol or misoprostol alone. Nevertheless, surgical methods have been shown a greater acceptability and patient satisfaction due to a reduced incidence of adverse effects. Currently, Manual Vacuum Aspiration (MVA) is the technique recommended by the Brazilian Ministry of Health and the Brazilian Federation of Gynecology and Obstetrics.

MVA should be performed after cervical ripening. This pre-surgical procedure makes the procedure safer and more effective. In Brazil, misoprostol is the most suitable drug to be used in these cases because of its efficacy, ease of use, low cost, stability at room temperature, and availability. Misoprostol is a synthetic prostaglandin E1 analog and can be administered by oral, sublingual, buccal, rectal, and vaginal routes.

Smaller doses, such as 200 µg, have not yet been tested enough in the literature, being a potential research line. Therefore, the objective of this study is to evaluate a Misoprostol dose of 200 µg compared to his standard dose of 400 µg.

JUSTIFICATION FOR THE PROJECT

The studies currently available in the literature are not conclusive as to whether there is greater efficacy in uterine cervical priming using misoprostol 200 µg compared to 400 µg. A prospective study will bring more information for further decision.

STUDY GOALS

Primary

To verify if a dose of 200 µg of misoprostol results in a cervical priming is not

less than 25% at the dose of 400 µg usually used.

Secondary

To verify if there is a relationship between the dose of misoprostol and the degree of cervical dilation (≥8mm / <8mm).

HYPOTHESIS

Our null hypothesis is that $P_{standard\ (400\mu g)} \geq P_{alternative\ (200\mu g)} + 25\%$;
Our alternative hypothesis is that $P_{standard\ (400\mu g} - 25\% < P_{alternative\ (200\mu g)}$.

Variables:

1. The control group (400 µg misoprostol);
2. The experimental group (200 µg misoprostol);
3. Cervical dilation present or not.

METHODS

Study design

This will be a triple-blinded, non-inferiority, two-arm parallel randomized clinical trial (RCT) at Hospital de Clínicas de Porto Alegre (HCPA), following the parameters of CONSORT[19].

Geographical and temporal limitation

The study will be carried out in patients seen at the gynecological emergency of HCPA. A period of 48 months will be allowed for data collection (5 cases of abortion per week).

Inclusion criteria

All patients presented at the HCPA gynecological emergency unit, aged between 18-50 years old, with an indication for manual vacuum aspiration (MVA) and the use of misoprostol, <12 weeks of gestation, without comorbidities will be invited.

Exclusion criteria

Patients who do not wish to participate in the project, have an ectopic pregnancy, with comorbidities (congestive heart failure, chronic obstructive pulmonary disease), with hypovolemic shock, with istmocervical insufficiency, who have an infection (fever, pus, leukocytosis [> 14000 leuc]), with a twin pregnancy, Marfan syndrome, allergic to misoprostol, with blood dyscrasia, who have an pervious cervical canal at the time of the consultation, those with previous surgery of the uterine cervix (conization) and concomitant use of IUDs will be excluded.

Randomization

Patients eligible for this study will be invited to participate in the research. After reading and signing the informed consent, patients will be submitted to a standardized interview and will be randomized to one of the two arms.

Patients will be randomly allocated to receive misoprostol 400 or 200 µg. Randomization list was obtained from a web-based site (www.randomization.com) and divided into blocks of four. The randomization sequence will remain in sealed, opaque, sequential envelopes.

Treatment

After randomization, one of the assisting researchers, one that will not perform the MVA procedure, will introduce the misoprostol into the vagina. A 200 µg misoprostol tablet will be inserted into the vaginal fornix. For reducing bias, a second mock introduction will performed in the 200 µg group. The 400µg group will have a double insertion. Medical staff that will perform the MVA will not be aware of the randomization.

Outcomes

The following outcomes will be determined:

1. Dilatation of the cervix without the need for a dilator between 3 and 6 hours after placing the misoprostol;
2. Dilatation of the cervix with 8mm. The measurement of cervical dilation will be done with a Karmann cannula, starting with the largest diameter (11 mm) and decreasing until it was possible to introduce, without resistance, the cannula into the uterine cavity (continuous variable 4 to 11).

Sample size

The sample size was calculated as a non-inferiority clinical trial according to the literature (Blackwelder 1982). We expected that cervical dilation would be achieved in 96% of the cases using 400 µg of misoprostol and 86% in the 200 µg group. If there is a true difference in favour of the 400 µg treatment of 10% (96% vs 86%), then at least 184 patients were required in order to be 95% sure that the upper limit of a one-sided 97.5% confidence interval (or equivalently a 95% two-sided confidence interval) would exclude a difference in favour of the standard group of more than 25%.

The determination of non-inferiority margins was based on the literature (Hahn 2012; Wu et al. 2017; Kapp et al. 2010; Singh et al. 1998). It is known that 400 µg of misoprostol yields a 96% cervical dilation > 8 mm (Singh et al. 1998). We considered 86% of the 200 µg misoprostol group as the minimal acceptable percentage. The non-inferiority margin was determined by ⅓ of the difference between the 400 µg effect (96.7%), compared to the 200 µg dose (23.3%) found in the literature, i.e. 73.4 / 3 = 24.46. (Fong, Singh, and Prasad 1998; Hahn 2012; Wu et al. 2017; Kapp et al. 2010; Singh et al. 1998).

Statistical analysis

Statistical analysis to be used will performed using Student's *t*-Test, after confirming the normal distribution of the sample, otherwise, a mathematical transformation of the data will be performed to obtain a Gaussian curve. If there is no statistical difference between the groups, cervical dilation between each group can be verified with the Pearson (or Spearman) test using the continuous variables of both groups (dilation), or the chi-square test dilation <8, ≥8mm. If there is a statistical difference between the groups, the correlations will be by groups, i.e., 400 µg and 200 µg.

Ethical considerations

This study was submitted to the HCPA Ethics and Research Committee, which assessed all aspects necessary for the proper conduct of the study.

Property of informations

Both patients' privacy and confidentiality will be preserved. Only general data will be released.

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SCHEDULE

If the CEP/HCPA is approved, it is expected to start activities in June 2016.

PHASES	***Period***
CEP appreciation / approval	May/2016
Data collect	June/2018-November/2021
Literature review	May/2017-March/2021
Data analysis and interpretation	December/2021
Writing for National Congress	December/2021
Submission of the article for submission to an indexed journal	December/2021

BUDGET

Funds will be requested from funding agencies (FAPERGS, CNPq, PROPESQ, FIPE).

Item	***Value in Reais (***R$)
Typing and article formatting	100,00
Spell check	120,00
Paper sheets (size: A4)	15,00
Printer ink	40,00
Total	**275,00**

APPENDIX 1

Informed Consent Form (Trial 16-0309)

We are conducting a study on a more effective way to perform uterine evacuation in cases of abortion. You are being invited to participate in this study, called “Randomized double blind clinical trial between Misoprostol 400 µg and Misoprostol 200 µg” in uterine dilation in cases of first trimester abortion.

The purpose of this study is to assess whether using a 200 µg dose of a drug called misoprostol can be equally effective at the dose currently used instead of 400 µg. This medication promotes uterine dilation, so that it is not necessary to use other instruments that do this mechanically.

In HCPA, misoprostol 400µg has been used for many years. It is possible that there is no difference between these two treatment doses, but this must be proven through a comparative study, like this one. If we verify that the use of a 200 µg dose has the same action as the pre-established dose, the lower dose may be adopted as a standard, reducing the possible side effects of this medication.

Your participation is completely voluntary. If you agree to participate in this study, you can be drawn to participate in one of two groups: the group in which the patients will receive 400 µg of the drug or the group that will receive 200 µg of the drug.

The next steps in the procedure will be performed equally on all patients. These drugs will be entirely free.

The possible side effects of this medication are: diarrhea, vomiting, nausea, fever and chills.

You are free to refuse to take part in this work. If there is a need to find out which medicine you took, it will be possible, without prejudice to your care.

There is no provision for any type of payment for participation in the study and the participant will have no cost with respect to the procedures involved.

The researchers are committed to maintaining the confidentiality and privacy of the participants' personal identification data, with the results being disseminated in a grouped manner, without identifying the individuals who participated in the study.

For clarification, you can call [redacted] or [redacted], speak with Dr. Ricardo Savaris responsible for the research.

The Research Ethics Committee can be contacted to clarify doubts, by calling [redacted], from Monday to Friday from 8 am to 5 pm).

This document is in two copies of equal content and value.

I, the undersigned, aware of the terms described above, agree to participate in this research.

Name of participant _____ Signature _____

Responsible name _____ Signature _____ (if applicable)

Researcher name_____ Signature_____ (the one who conducted the consent process)

Place and date:_____

MISOPROSTOL-200 PROJECT PROTOCOL 16-0309

Paste patient label on here

Patient's name: _____ Age:_____

Hospital Registration:_____ Telephone:_____

Date of admission: _____/_____/_____ Discharge date:___/____/____

White ( ) Black ( ) Brazilian Indian ( ) Asian ( )
Gesta: Para: Miscarriage:

Approximate gestational age : _____

Inclusion criteria

Has indication for uterine evacuation	Yes( ) No ( )
GESTATION < 12 WEEKS	Yes( ) No ( )

Any **NO** excludes

Exclusion Criteria (Yes):

Do you have any comorbidity (congestive heart failure, chronic obstructive pulmonary disease?	Yes( ) No ( )
Are you allergic or did you use misoprostol?	Yes( ) No ( )
Do you use an IUD?	Yes( ) No ( )
Have you had previous cervical surgery (conization)?	Yes( ) No ( )
Is it an ectopic pregnancy?	Yes( ) No ( )
Is she in hypovolemic shock?	Yes( ) No ( )
Do you have cervical incompetence?	Yes( ) No ( )
Does patient have infected abortion (presence of fever, cervical pus, leukocytosis [> 14000])?	Yes( ) No ( )
Is it a twin pregnancy?	Yes( ) No ( )
Do you have Marfan syndrome?	Yes( ) No ( )
Patient with coagulopathy?	Yes( ) No ( )

Patient with cervical os opening (4 mm dilation at the time of consultation)?	Yes( ) No ( )
History of intrauterine manipulation with contaminated objects.	Yes( ) No ( )

Sign the consent form
Prescribing randomized medication from project 16-0309 WITH

Randomization: Treatment # _____, placed at ____:_____

INITIATION OF THE PROCEDURE: ____:____

Outcome: adequate dilation for the procedure ( ) Karmann
cannulas # used:
Dilation NOT suitable for procedure ( ) Hegar
dilators # used:
Adverse events/observations: