

**TITLE: A Randomized Double-blinded Comparison of 24-hour interval
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Misoprostol for Cervical Preparation in Second-Trimester Surgical Abortion**

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A Randomized Double-blinded Comparison of 24-hour interval-Mifepristone and Buccal Misoprostol versus Mifepristone and Vaginal Misoprostol for Cervical Preparation in Second-Trimester Surgical Abortion

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1. Abstract

Patient preference for medications in place of osmotic dilators as cervical preparation is well known. Twenty-four to 48 hours following mifepristone, vaginal and buccal misoprostol have demonstrated equal efficacy in second-trimester medical abortion but have not been compared as cervical preparation for second-trimester surgical abortion.

This study will randomize participants undergoing a second-trimester surgical abortion between 16 0/7-20 6/7 weeks gestation to 200mg mifepristone followed 20-24 hours later with 400mcg vaginal misoprostol and buccal placebo versus 400mcg buccal misoprostol and vaginal placebo 1-2 hours prior to the procedure. Primary outcome is intraoperative procedure time as measured by time of first instrument in the uterus (dilator if further dilation is required or forceps if no further dilation required) to last instrument out of the uterus. The study uses a superiority design and is powered to detect a 4-minute difference in procedure time from a baseline of 10 ± 5 minutes with 90% power and two-tailed alpha of 0.05 requiring 33 participants in each arm. To account for 10% dropout or disqualification, 72 participants will be recruited. Secondary outcomes include cervical dilation assessed with largest Pratt dilator initially accepted without resistance, patient report of pain (as measured on an 11-point VAS scale), side effects, acceptability, and recommendation to friends (as measured on a 5-point Likert scale), and provider estimation of blood loss, complications, ease of dilation (as measured on an 11-point VAS scale), acceptability, and recommendation to other patients (as measured on a 5-point Likert scale).

2. Specific Aims

This study aims to compare mifepristone and buccal misoprostol to mifepristone and vaginal misoprostol for cervical preparation for second trimester D&E. We hypothesize that giving oral mifepristone 20–24 hours and vaginal misoprostol 1–2 hours prior to D&E will provide better cervical dilation than mifepristone 20–24 hours and buccal misoprostol 1–2 hours prior to D&E. The primary outcome of the study will be length of procedure as measured by first instrument in the uterus (dilator if further dilation is required or forceps if no further dilation required) to last instrument out of the uterus. Secondary outcomes will include cervical dilation achieved as measured by the largest size Pratt dilator accepted without resistance prior to the start of the procedure, total dilation required, blood loss, pain, complications, provider assessment of difficulty, and provider and patient acceptance and recommendation for other patients.

3. Previous research

The addition of mifepristone, a progesterone antagonist, to a misoprostol regimen has been shown to significantly decrease the medication-to-abortion interval in second-trimester induction terminations.¹ Vaginal administration has demonstrated improved dilation as compared to buccal administration but it is known that patients prefer buccal administration.² A comparison of mifepristone and vaginal versus mifepristone and buccal misoprostol has not been studied prior to second-trimester surgical abortion.

A Cochrane review (2010) of cervical preparation for second-trimester D&E did not recommend mifepristone and misoprostol for cervical priming due to high rates of pre-procedural expulsions.³ However, the primary basis for this conclusion is the trial by Carbonell et al. in which the 48-hour interval between the medications accounts for the high out-of-facility expulsion risk.⁴ A retrospective cohort of over 200 women between 14 and 19 6/7 weeks gestation showed no difference in difficulty of cervical dilation for patients receiving mifepristone 24–48 hours misoprostol as compared to osmotic dilators prior to surgical abortion. Two out of facility expulsions occurred in the mifepristone-misoprostol arms but the timing of medication to expulsion interval is not reported.⁵

More recent studies have limited the timing of mifepristone to 24 hours or less prior to procedure. Mifepristone only has been shown to provide adequate cervical dilation as compared to osmotic dilators to 16 weeks gestation with noninferiority design to detect a 3-minute difference in procedure time.⁶ A 24-hour interval between 200mg mifepristone and 400mcg buccal misoprostol has been shown as non-inferior to osmotic dilators for total procedure time for 15–18 week surgical abortions.⁷ Mifepristone and one-set of osmotic dilators was found to be non-inferior for total procedure time as compared to two sets of osmotic dilators for surgical abortion 19–23 6/7 weeks gestation.⁸

The addition of mifepristone has benefit as a cervical priming agent as an adjunct or alternative to osmotic dilators for surgical abortion, but it is not known whether the addition of vaginal versus buccal misoprostol changes cervical dilation and thus procedure time outcomes.

4. Rationale

Second-trimester dilation and evacuation (D&E) procedures at 14 weeks or greater require cervical preparation.⁹ Osmotic dilators have traditionally been used for cervical dilation but it is known that patients prefer medication to dilators.¹⁰ Misoprostol alone can be used for early second trimester dilation but is associated with increased requirement for dilation.¹¹ Adding mifepristone to buccal misoprostol was found to be non-inferior to osmotic dilators for procedure time for 15-18 weeks gestation.⁷ Mifepristone alone was found to provide adequate cervical preparation up to 16 weeks gestation.⁶ Vaginal misoprostol is associated with fewer gastrointestinal side effects as compared to buccal administration and is associated with a shorter induction to delivery interval.¹² This study aims to evaluate mifepristone and buccal versus mifepristone and vaginal misoprostol (with an interval of at least 20 hours between the medications) for gestational ages 16 0/7 to 20 6/7. This study will contribute to the literature evaluating medication only cervical preparation prior to second-trimester procedures.

5. Research design and General Methodological Approach

We have chosen a randomized controlled trial to ensure that neither patient nor provider will be biased by medication choice. Seventy-two English or Spanish-speaking women greater than 18 years of age and at 16 0/7-20 6/7 weeks gestation will be enrolled with 36 women in each arm.

Computer-generated randomization will be utilized to assign treatment arms and the vaginal misoprostol and buccal placebo and buccal misoprostol and vaginal misoprostol will be prepared according to randomization scheme by the research pharmacy in opaque-sealed envelopes as to blind participants and providers.

One arm will receive mifepristone 200mg orally 20-24 hours prior and misoprostol 400mcg (two 200mcg tablets) vaginally 1-2 hours prior and placebo (two lactose tablets designed to appear similar to misoprostol) buccally 1-2 hours prior to D&E. The second arm will receive mifepristone 200mg orally 20-24 hours prior and misoprostol 400mcg (two 200mcg tablets) buccally and placebo (two lactose tablets designed to appear similar to misoprostol) vaginally 1-2 hours prior to surgical abortion. The patients will place the tablets in the pre-operative area from pre-marked envelopes. The patient will be instructed to take the medication in the envelope marked buccally (misoprostol 400 mcg or placebo) to be placed in the cheek pouch for 30 minutes and then remaining swallowed and the envelope marked vaginally (misoprostol 400mcg or placebo) to be placed vaginally as far as the patient can insert with her finger. The patient will be witnessed taking the buccal medication but the patient will be given privacy for vaginal administration. The time will be recorded in the patient's chart. Prior to the procedure, patient assessment of medications will be obtained as detailed in 5.5.

At 1-2 hours after misoprostol and placebo administration, the participant will be brought into a procedure room for a dilation and evacuation (D&E). Prior to the D&E, an assessment of cervical dilation will be made as assessed by largest size Pratt dilator accepted without resistance starting with 39-French. Only the attending will assess cervical dilation but procedures will be performed by the attending and residents-in-training. Type of provider will be recorded.

Five time estimates will be recorded: 1) time interval between mifepristone and misoprostol/placebo placement, 2) time interval between misoprostol insertion and assessment of cervical dilation 3) total procedure time (speculum in to speculum out), 4) intraoperative procedure time designated as start of additional dilation (if required) or start of uterine instrumentation (if further dilation not required) to time of last instrument removed from uterus. Following the procedure, provider assessment will be obtained as detailed in section 5.5.

5.1 Criteria for selection of subjects

The trial will be conducted at Virginia Commonwealth University Medical Center (VCUHS) and Virginia League of Planned Parenthood (VLPP) over the course of approximately fourteen months. The study will enroll healthy women, over 18 years of age, eligible for non-urgent D&E at 16 0/7 weeks to 20 6/7 weeks gestation, confirmed by sonogram. Patients presenting to either office in consultation for a D&E will be recruited for participation. Exclusion criteria will include: emergent need for D&E, intrauterine infection, fetal demise, molar pregnancy, multiple pregnancy, uterine anomaly or significant distortion of the uterus with fibroids, intolerance, allergy or contraindication to mifepristone or misoprostol.

5.2 Subject recruitment and allocation

Both VCUHS and VLPP serve representative samples of Richmond, Virginia. Second trimester services at VLPP started in 03/2014.

After the patient has completed the counseling process and decided to proceed with an induced abortion, she will be approached by either a co-investigator or research staff member and asked to participate in the study. A detailed explanation of the study will be provided and informed consent obtained in English or Spanish, according to patient preference. A copy of the informed consent will be given to the patient. Eligibility for the study will be confirmed.

The VCU Investigational Research pharmacy will prepare the allocation sequence for preparation of allocation envelopes. Subjects will be allocated in blocks of 4-6. A researcher not involved in subject recruitment and without participant contact will prepare sequentially numbered opaque envelopes with the assigned, blinded pills for vaginal or buccal administration (misoprostol or placebo) enclosed. The envelope will not contain information that would reveal the group assignment. The envelope will not be assigned to a participant until eligibility is confirmed. The envelope will not be opened until just prior buccal and vaginal placement. The allocation number will be recorded twice in the participant's chart. The envelope will be attached to the chart. The envelope will only have the allocation number on the outside and the blinded pills inside.

5.3 Description of the drugs and devices to be studied

Mifepristone is a progesterone receptor antagonist. The brand name Mifeprex is manufactured for Danco Laboratories, LLC with address: 640 5th Avenue Floor 13 New York, NY 10019. The dose of mifepristone to be utilized in this study is 200 mg.

Misoprostol is a synthetic prostaglandin E1 analogue. Generic misoprostol is manufactured by Taj Pharmaceuticals Ltd. with address as follows: Plot No. 32/2B, Village Tondali, Taluka-Khalapur, Dist. Raigarh, Maharashtra-410 203 India (US FDA approved manufacturer). Brand name misoprostol, Cytotec, is manufactured by Pfizer, Inc. with address: 235 East 42nd Street New York, NY 10017-5703. The dose of misoprostol to be utilized in this study is 400 mcg.

Both misoprostol and placebo pills will either be encapsulated or will be supplied in a troche. This is to be determined. They will be created by the VCU investigational research pharmacy: VCU research pharmacy: 410 North 12th Street, P.O. Box 980581, Richmond, Virginia 23298-0581

5.4 Admission procedure

Recruitment will begin July 2015 and extend for approximately fourteen-months, ending once enrollment is complete. Patients presenting to VCUHS or VLPP will be enrolled, as described in 5.2. Following enrollment, the patient will complete an admission form including baseline demographics and reproductive history.

After ensuring the patient meets eligibility criteria, has signed consents and following the preoperative assessment, a research staff member will give the patient mifepristone 200mg to take orally in the staff member's presence and the time will be recorded in the patient's chart. The following day, a research assistant will dispense two numbered (one vaginal and one buccal) envelopes as described in 5.2 upon arrival to VCU Medical Center for the procedure. Prior to dispensing the envelope, the research staff member will examine the allocation numbers as recorded in the patient's chart to ensure a match.

5.5 Patient and Provider Assessment

The patient will complete the survey immediately prior to the procedure to provide an accurate assessment of medication acceptability and side effects prior to anesthesia. The patient survey will assess pain (as measured using an 11-point visual analog scale) and acceptability of treatment with respect to ease of use, side effects, and recommendation to others (as measured using a 5-point Likert scale).

The provider will complete the assessment immediately following the procedure. The provider assessment elicits estimated blood loss, complications, ease of cervical dilation (with responses rated on an 11-point visual analog scale), procedure difficulty, recommendation for same patient and recommendation for other patients (as measured using a 5-point Likert scale).

5.6 Criteria for discontinuation

Any participants who meet any one of the following criteria at any point after enrollment will be discontinued from the study:

- Urgent need for a D&E
- Decision not to proceed with the D&E
- Decision to stop participation in the study

5.7 Data management

Data will be entered by the research coordinator and stored on a computer at each center accessible only to the primary and co-investigators and research coordinator via password protection.

5.9 Data analysis

STATA statistical software (StataCorp LP, College Station, TX, www.stata.com) will be used to analyze the baseline characteristics of the populations based on the study questionnaires completed by participants prior to their procedure. Primary and secondary outcomes will be recorded as described above in 5.4. Both primary and secondary outcomes will be analyzed using t-tests or appropriate non-parametric comparison tests as appropriate. The perception assessments (VAS) will be assessed using non-parametric analysis. The primary analysis will be based on intention to treat.

5.10 Number of subjects and statistical power

Sample size is based on prior studies assuming that longer procedure times reflect a need for further dilation and manipulation. Procedure time is defined in this study as first instrument passing into the uterus until last instrument out of the uterus. Previous studies have defined a 3-minute for 14–16 week gestations or 5-minute change for 19–24 week gestations as clinically significant.⁶ For this study evaluating 16 – 20 6/7 week gestations, we chose 4-minute difference as clinically significant. Using a superiority design, in order to detect a 4-minute change in procedure time from a baseline of 10 minutes with a standard deviation (SD) 5 minutes), with a two-tailed alpha of 0.05 and power of 90%, 33 women will be needed in each arm. We plan to recruit 72 participants due to post-enrollment exclusion.

5.11 Study limitations

While there are many possible regimens of mifepristone and misoprostol, which could be compared, we have tried to select the most reasonable and practical regimen for use in our setting. Additional studies may be needed in the future to compare other regimens. As this study will recruit patients from VCU Medical Center and Virginia League of Planned Parenthood, the study may be generalizable only to patients of similar characteristics. However, since the biologic response to mifepristone and misoprostol is not known to vary significantly, the results should be widely generalizable. Loss of blinding is a concern. Steps have been taken to ensure internal validity in that both participants and practitioners will be blinded to allocation of treatment versus placebo. We will ask both providers and participants which group they believe the participant was in to determine if group assignment was detectable.

Limitations of this study will include potential extension of time for recruitment and a relatively small sample size.

6. Links with other projects

There is a multicenter trial comparing the addition of mifepristone versus misoprostol to osmotic dilators versus dilators alone.

7. Expected outcomes of the study and dissemination of findings

If 20–24 hour mifepristone and 2–4 hour misoprostol produces better cervical dilation than misoprostol only for second trimester D&E's, this regimen could increase the medication only options for surgical procedures. We plan on publishing the study in a reproductive health journal and giving oral presentations of results.

8. Budget justification

8.1. Personnel

Principal investigator: Frances Casey will assist in subject recruitment, obtaining consent, data analysis, dissemination of findings, and performing procedures related to data acquisition. The following physicians will also assist in subject recruitment and obtaining consent: Randi Falls. The research coordinator will be a paid position. He/she will assist in subject recruitment, obtaining consent, treatment allocation and concealment. We anticipate supplementing an existing research coordinator for approximately \$5,755 with 34.3% fringe. Please see attached budget document for further details.

8.2. Equipment

We anticipate utilizing the ultrasound machine and computers currently available at the study sites.

8.3. Materials and Supplies

These include the cost of the medication and placebo, concealment for misoprostol and placebo, envelopes. The total is \$7,161

8.4. Participant Incentives

Each participant will receive a \$10 Target gift card as reimbursement for time after completion of the study, approximately \$720.

8.5. Travel

No travel reimbursement required.

9. Timeline

Recruitment will begin July 2015 and extend for approximately 9-months or once enrollment is complete. As recruitment will occur on patient's initial consultation for procedure and allocation and assessment will occur on the day of procedure, data collection will be complete the day of the patient's procedure. Data analysis will follow and will complete prior to the writing of the final report-please see timeline attached.

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