CLINICAL STUDY PROTOCOL

FOR DRUG/DEVICE/BIOLOGIC RESEARCH

Prophylactic Analgesic and Antiemetic Regimen for Medical Abortion < 70 days

Version 5

1/20/2023

Study Personnel

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Protocol Amendment History

Version	Date	Description
Original version	4/1/22	Original submission
2	9/17/22	Edits made as requested by IRB
3	11/19/22	Edits made as requested by IRB: - Clarification on informed consent process (section 9.7) - Clarification on when the patient's medical information will be collected and stored in red cap (section 6.1 and 6.6) - Length of time patient's records will be stored in encrypted redcap changed from 6 years to 2 years
4	12/28/22	Addendum of section 9 as per request by IRB. HIPAA alteration statement removed from proposal.
5	1/20/23	- Clarification on recruitment of study (section 6.3) - Time frame of study changed given IRB approval not yet obtained (section 4.1.1)

Summary

Study Description	Randomized trial which will aim to evaluate whether prophylactic use of ondansetron and ibuprofen will decrease side effects associated with medical abortion and increase patient satisfaction
Objectives	- Determine if prophylactic use of ondansetron and ibuprofen during medical abortion treatment can increase patient satisfaction thereby creating a more favorable outcome - Evaluate for ideal pain and anti-nausea management regimen for medical abortion
Endpoints/variables	- Nausea and pain scale at 6-8hour mark and 24 hour mark after administration of misoprostol - Patient report of satisfaction with the experience and likelihood to recommend a similar regimen to others
Study Population	Healthy, English speaking 18-50 year old female volunteers undergoing medical abortion whether for voluntary interruption of pregnancy or missed abortion
Phase	n/a. the medications given in this study are part of the standard of care when treating side effects of medical abortion.
Description of sites (facilities enrolling patients)	HUMC OBGYN Faculty Practice
Study duration	March 2023- November 2023
Participant duration	2-3 weeks (includes follow up appointment)
Schedule of activities	- Subjects seen in office and enrolled in study - Subjects take misoprostol 24 hours after taking mifeprex and will either take ibuprofen and ondansetron prophylactically or not - Subjects will record their pain and nausea score at the 6-8 hour mark and the 24 hr mark - Subjects will return to the office for follow up

Follow up / End of study definition	Each patient will have a follow up visit 2 weeks after participation to discuss their experience End of study: after 168 subjects have be enrolled or at end of November 2023

1 – Introduction

There is currently an ACOG recommended regimen for successful medical abortion however there is no official recommendation for management of associated side effects related to this process. The use of analgesic medications including ibuprofen and antiemetics including ondansetron are common in the management of said side effects. Our study aims to determine if prophylactic use of ondansetron and ibuprofen during medical abortion treatment can increase patient satisfaction thereby creating a more favorable outcome

2 – Background

The recommended regimen for medical abortion up to 70 days GA is 200mg of oral mifepristone followed by 800mcg of misoprostol administered either buccally, vaginally, or sublingually. While the efficacy of medical abortion is greater than 90%, there are considerable unpleasant side effects associated with these agents (1). Patients often consider these potential side effects when electing for medical vs surgical management for medical abortion (2). Nausea, vomiting and pain are common side effects of misoprostol, particularly when taken orally (3). The most severe pain is reported to occur about 2.5-4hrs after misoprostol use, lasting about 1 hour in duration (4).

While there is a recommended regimen for successful medical abortion, there is no official recommendation for management of the above associated side effects. According to the WHO, research is needed to evaluate the ideal pain management regimen for medical abortion, including additional medications and timing of medication administration (5). Livshits et al found that ibuprofen is more effective than acetaminophen to reduce pain (6). Ibuprofen is commonly taken as therapeutic management for pain rather than prophylactically to prevent or decrease the intensity of pain experienced during medical abortion. Prior studies have assessed pre-emptive analgesia in the setting of medication abortion. Avraham et al found that pre-emptive ibuprofen treatment was found to be more effective than a placebo in pain prevention (7). Dragoman et al also investigated preemptive pain control administration with tramadol or ibuprofen/metoclopramide and found lower mean maximum pain scores in both experimental groups compared to placebo. Nonetheless, the lower mean maximum pain scores did not achieve clinical significance (8). Despite these findings, they concluded that ibuprofen, tramadol, and metoclopramide should be considered for prophylactic pain management in medical abortions.

Ondansetron is another antiemetic that has been shown to be more effective than metoclopramide when managing postoperative nausea after laparoscopic cholecystectomy as well as chemotherapy induced nausea and vomiting (9,10). We hypothesize that prophylactic use of ondansetron and ibuprofen will increase overall patient satisfaction and decrease mean pain and nausea scores during the medical abortion process.

3 – Rationale, Objectives and Hypothesis

3.1. Study Rationale/Problem Statement/Research question or Study significance

Determine if prophylactic use of ondansetron and ibuprofen during medical abortion treatment can increase patient satisfaction thereby creating a more favorable outcome

3.2. Hypothesis (if applicable)

The prophylactic use of ondansetron and ibuprofen will increase patient satisfaction during medical abortion treatment

3.3. Primary Objective

Determine if prophylactic use of ondansetron and ibuprofen during medical abortion treatment can increase patient satisfaction thereby creating a more favorable outcome

3.4. Primary Outcome Variable(s)

Patient satisfaction rating (see below for rating tool)

3.5. Secondary Objective(s) (if applicable)

Evaluate for a satisfactory pain and anti-nausea management regimen for medical abortion

3.6. Secondary Outcome Variable(s) (if applicable)

Maximum pain and nausea score in first 24 hours, need for additional anti-emetics/analgesics

4 - Study Design

4.1 General Design

This study is a randomized trial which will involve tow study groups. One group will be the intervention group which will be asked to take ibuprofen and ondansetron at the time of misoprostol administration. The second group will be the control group which will be asked to take ibuprofen or ondansetron only when experiencing pain or nausea respectively.

4.1.1 Study Duration

Data collection will take place from March 2023 to November 2023

Data will be analyzed from March 2023 to November 2023

4.1.2 Participant duration

Approximately 2 weeks

4.1.3 Number of Study Sites

Hackensack University Medical Center

5 – Study population

5.1. General description

- Healthy, English speaking 18-50 year old female volunteers undergoing medical abortion whether for voluntary interruption of pregnancy or missed abortion

5.2. Number of Participants

- 168 total based on power analysis: Two independent study groups, continuous, group 1 mean 7 (+/- 3), group 2 mean 5.5, alpha 0.05, power 0.9

5.3. Eligibility Criteria

- Inclusion criteria: Healthy, English speaking 18-50 year old female volunteers undergoing medical abortion whether for voluntary interruption of pregnancy or missed abortion
    - GA </= 70 days confirmed via ultrasound
    - Access to a time keeping device
    - Willingness to complete a telephone or in-clinic follow up
- Exclusion criteria: chronic medical problems including but not limited to cardiac conditions, malignancy or organ damage
    - Failed medical abortion resulting in surgical management
    - Known intrauterine infection
    - Known allergy to ondansetron or ibuprofen
    - Subjects chronically receiving analgesic drugs
    - Subjects unable to give consent
    - Subjects taking medications that interact with ondansetron or ibuprofen

5.3.1. Pregnancy, Breastfeeding and Contraception requirements (if applicable): see above

5.3.2. Vulnerable populations (if applicable): not applicable

5.3.3. Withdrawal criteria (as applicable)

Patient who fail medical management and need surgical management. These patients will be withdrawn from the study and replaced.

6 – Study intervention (drug/device/biologic)

6.1. General description

- Eligible patients seeking medical abortion treatment during appointments with a family planning specialist will be verbally given information about the study. Those who express interest will undergo a detailed informed consent process.
- Consent and counseling will be available in English only
- Counseling on medication abortion for each patient will be standardized. Each patient will be provided instructions to go home with
- Randomized controlled trial
    - Randomly assign treatments in a 1:1 ratio.
    - Patients will be given mifepristone in the clinic
    - Will be given 800mcg of misoprostol and instructed to insert vaginally.
    - The intervention group will be instructed to take ibuprofen and ondansetron with the misoprostol as a prophylactic measure
    - The control group will be instructed to take ibuprofen or ondansetron only when experiencing pain or nausea respectively
- Information on the patients demographics (age, race, ethnicity, gravity and parity, obstetrical history, BMI) will be recorded as well as gestational age at time of administration and diagnosis (missed abortion vs elective termination of pregnancy). This will be recorded and kept in the encrypted RedCap system after patient agrees to participate in the study.
- Subjects will also be asked their mean pain score on a numerical pain scale of 1-10 during their menstrual cycles as well as need for analgesia during menstruation.
- Subjects will be asked if they are experiencing nausea or vomiting prior to starting the study. They will also be asked if they have a history of bariatric surgery, baseline reflux, conditions that can predispose them to nausea/vomiting
- Subjects will be asked to record their nausea and pain level using a numerical scale rating at the 6-8 hour mark after administration of misoprostol. After 24 hours of administration, they will be asked their maximum pain score over the course of the first 24 hours. The subjects will have the option to either record their pain scores in a log or to text their pain scores directly to a designated phone number. Contact via text message will be encouraged as this will allow for live feedback and reduce recall bias
- Researchers will contact participants 3-5 days thereafter to collect and/or verify information on their pain and nausea scales and determine adherence to treatment regimen. They will also collect information on supplemental analgesia and antiemetics that may have been used.
- Subjects will be asked how satisfied they were with their overall experience (Very satisfied/Fairly satisfied/Neither satisfied nor dissatisfied/Fairly dissatisfied/Very dissatisfied). They will also be asked how likely they are to recommend this pain/antiemetic regimen method to a friend (Extremely likely/Likely/Neither likely nor unlikely/Unlikely/Extremely unlikely /Don’t know).

- Ask the patient to return for follow up visit to determine abortion status.
    - Information on successful abortion will also be collected at the follow up visit

6.2. Screening and screen failures: not applicable

6.3. Recruitment, enrollment and retention (including screen failures as applicable)

Eligible patients seeking medical abortion treatment during appointments with a family planning specialist will be verbally given information about the study by the provider. Those who express interest will undergo a detailed informed consent process.

6.4. Study intervention

6.4.1 Dosing and Administration:

Intervention arm: patients will be instructed to take the ibuprofen 600mg and ondansetron 4mg at the time of misoprostol administration. The ondansetron dose is the minimum amount that can be administered at a given time. The ibuprofen dose is the standard recommended in our office currently for pain management for patients ungoing medical abortion.

No intervention arm: patients will be instructed to take misoprostol and take 600mg of ibuprofen for pain as need or ondansetron 4mg as needed for nausea

6.4.2. Dose modification (if applicable): patients will be instructed on the appropriate time interval in which they can take additional medication for pain or nausea if required

6.4.3. Schedule of events (schema)

- Subjects seen in office and enrolled in study (clinical visit)
- Subjects take misoprostol 24 hours after taking mifeprex and will either take ibuprofen and ondansetron prophylactically or not
- Subjects will record their pain and nausea score at the 6-8hr mark and the 24hr mark

- Subjects will return to the office for follow up (clinical visit)

6.4.4. Study visits (only if study has multiple visits, explain what will happen in each visit, dosing, assessments etc.)

1. First visit: patient will be seen in the office for medical management of missed abortion. The treatment will be explained to them as well as the study itself and instructions on how to take medication to manage side effects. Will be instructed to take the medication prophylactically vs when in pain

2. Follow up visit after medical abortion to determine if abortion was successful as well as to discuss the overall experience

6.5. Assignment / randomization (if applicable): patient will be randomly assigned on a 1:1 ratio using a random number generator

6.6. Data collection (data points, source and storage)

- Information on the patients demographics (age, race, ethnicity, gravity and parity, obstetrical history, BMI) will be recorded as well as gestational age at time of administration and diagnosis (missed abortion vs elective termination of pregnancy)
- Subjects will also be asked their mean pain score on a numerical pain scale of 1-10 during their menstrual cycles as well as need for analgesia during menstruation.
- Subjects will be asked to record their nausea and pain level using a numerical scale rating at the 6-8 hour mark after administration of misoprostol. After 24 hours of administration, they will be asked their maximum pain score over the course of the first 24 hours. The subjects will have the option to either record their pain scores in a log or to text their pain scores directly to a designated phone number. Contact via text message will be encouraged as this will allow for live feedback and reduce recall bias
- Subjects will be asked how satisfied they were with their overall experience (Very satisfied/Fairly satisfied/Neither satisfied nor dissatisfied/Fairly dissatisfied/Very dissatisfied). They will also be asked how likely they are to recommend this pain/antiemetic regimen method to a friend (Extremely likely/Likely/Neither likely nor unlikely/Unlikely/Extremely unlikely /Don't know).
- Data from the survey will be stored in the secure encrypted database of red cap when it is obtained

6.7. Concomitant medication (if applicable): the medications for medical abortion itself, mifeprex and misoprostol

6.8. Preparation/ Handling/ Product storage (and stability if applicable)/ Accountability: n/a

6.9. Packaging and labeling (if applicable): n/a

6.10. Follow-up and end-of study (if applicable)

- Researchers will contact participants 3-5 days thereafter to collect and/or verify information on their pain and nausea scales and determine adherence to treatment regimen. They will also collect information on supplemental analgesia and anti-emetics that may have been used.
- Patients will be asked to return for follow up visit to determine abortion status. Information on successful abortion will also be collected at the follow up visit.

6.11. Study discontinuation (if applicable): if adverse events occur during the study

6.12. Risks

Risk of taking additional medication for management of pain and nausea if ibuprofen or ondansetron is taken prophylactically.

Risk of taking ibuprofen as stated on box:

Cardiovascular Thrombotic Events

Non-steroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use.

Ibuprofen Tablets is contraindicated in the setting of coronary artery bypass graft (CABG) surgery.

Gastrointestinal Risk

NSAIDS cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.

Risk of taking ondansetron as stated on box:

Get emergency medical help if you have signs of an allergic reaction to ondansetron: rash, hives; fever, chills, difficult breathing; swelling of your face, lips, tongue, or throat.

Common ondansetron side effects may include: diarrhea or constipation, headache, drowsiness, or tired feeling.

Risk of breach of confidentiality

6.12.1 Mitigation of risk (if applicable): will instruct subjects on the maximum dose of each medication so as not to exceed the daily maximum value

6.13. Benefits

6.13.1 Benefits for study participants: possible increased overall satisfaction with process of medical abortion. Less pain and nausea associated with treatment given medications are taken before experiencing pain or nausea

6.13.2 Benefits for society: develop an ideal pain and anti-nausea management regimen for medical abortion which may benefit others in the future

7 – Study Assessments and Procedures

7.1. Safety Assessment

A check in will be done with the subjects 3-5 days after treatment and a follow up appointment will be made 2 weeks after completion of treatment to ensure successful medical management and patient well-being. Should a patient require other interventions such as be admitted for acute blood loss anemia secondary to heavy bleeding during medical abortion or require surgical intervention due to failed medical management, this will be recorded in the subject record. The study does not increase their risks of having complications related to medical abortion itself. This

study is extremely safe, the only additional risk to the subject is taking an additional dose of ibuprofen or ondansetron for management of side effects related to medical abortion.

7.2. Efficacy Assessment

- Subjects will be asked to record their nausea and pain level using a numerical scale rating at the 6-8 hour mark after administration of misoprostol. After 24 hours of administration, they will be asked their maximum pain score over the course of the first 24 hours. The subjects will have the option to either record their pain scores in a log or to text their pain scores directly to a designated phone number. Contact via text message will be encouraged as this will allow for live feedback and reduce recall bias
- Researchers will contact participants 3-5 days thereafter to collect and/or verify information on their pain and nausea scales and determine adherence to treatment regimen. They will also collect information on supplemental analgesia and antiemetics that may have been used.
- Subjects will be asked how satisfied they were with their overall experience (Very satisfied/Fairly satisfied/Neither satisfied nor dissatisfied/Fairly dissatisfied/Very dissatisfied). They will also be asked how likely they are to recommend this pain/antiemetic regimen method to a friend (Extremely likely/Likely/Neither likely nor unlikely/Unlikely/Extremely unlikely /Don't know).
- Ask the patient to return for follow up visit to determine abortion status.

7.3. Other Assessment (if applicable): n/a

7.4. Unanticipated Problems, Adverse Events and Serious Adverse Events

7.4.1. Definitions: see above, the study does not increase the risks associated with medical abortions. The main adverse event to be alert for are patient's with unknown allergies to ibuprofen or ondansetron.

7.4.2. Grading/ Classification: n/a

7.4.3. Expectedness: n/a

7.4.4. Reporting: if there is an adverse event it will be reported to the IRB

8 – Statistical Considerations

8.1. Statistical Hypothesis

Prophylactic use of ondansetron and ibuprofen will lead to statistically significant lower pain and nausea scores during medical abortion treatment and will increase patient satisfaction scores.

8.2. Sample size consideration: Plan for 168 subjects in total. Power analysis: Two independent study groups, continuous, group 1 mean 7 (+/- 3), group 2 mean 5.5, alpha 0.05, power 0.9

8.3. Statistical Analysis Plan

Intention to treat analysis will be performed. Analysis will be completed at the end of the study.

9 - Trial Administration

9.1. Ethical Considerations

The study will be conducted according to the International Conference on Harmonization (ICH), Good Clinical Practice (GCP), the Declaration of Helsinki, Institutional Review Boards (IRB) and in accordance with the U.S. Code of Federal Regulations on Protection of Human Rights (21 CFR 50).

9.2. Institutional Review Board (IRB) Review (list the IRB of record): This study will be submitted to the Hackensack Meridian Health IRB

9.3. Protocol Adherence and Protocol Amendments: n/a

9.4. Data and Safety oversight

The Principal Investigator and the Co-Investigators will be responsible for the data and safety monitoring of this trial. This study is considered a minimal risk study which will have real-time monitoring by the PI and study team.

The Principal Investigator and the Co-Investigators will review the data, including safety monitoring, at [study specific] meetings and on an on-going/as needed basis at teleconferences. All Severe Adverse Events (SAEs) are required to be reported to the IRB.

9.5. Data management (collection, storage etc.): data will be collected and stored in RedCap

9.6. Privacy and Confidentiality

Data will be kept in the encrypted RedCap system. Each subject will be given a code to maintain confidentially. Only the members of the research team will have access to the data.

9.7. Informed consent: Informed consent will be obtained prior to enrollment into the study when the patient seeking medical abortion treatment during appointments with a family planning specialist. The patient will be given information about the study. Those who express interest will undergo a detailed informed consent process.

The patient’s permission to use and share the information and data from this study will not expire. The patient may cancel this Authorization at any time by notifying the research team in writing. If the patient cancels this Authorization, the study doctor and staff will not use any new health information for research. However, researchers may continue to use the health information that was provided before the patient cancelled the authorization.

Not signing the consent form or later canceling permission will not affect the subject’s

health care treatment outside the study, payment for health care from a health plan, or ability to get health plan benefits. However, if the subject does not give permission to use your health information, the subject may not take part in this study because their health information is needed in order to conduct the research.

9.8. Data Quality Assurance (if applicable)

All members of the research team will be trained to counsel the subjects on the study in a way that will make counseling standardized. Each subject will also be provided with instructions to go home with.

9.9. Study Records (retention etc.)

Records will be retained in accordance with regulatory, organizational and sponsor requirements, but for no less than two (2) years following the completion of the research. Disposal of records will be done in such a manner that no identifying information can be linked to research data.

9.10. Credentials, Training: n/a

9.11. Financing and Insurance (if applicable): n/a

9.12. Publication Plan and Data Sharing Plan: plan to publish data in peer-reviewed journal

9.13. Conflict of Interest (if applicable): no conflict of interest