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Scheduled Prophylactic Anti-emetics for Reduction of Emesis with Doxycycline (SPARED) Trial – Study Protocol

Principal Investigator:
Sarah Betstadt, MD MPH
Department of Obstetrics & Gynecology
University of Rochester Medical Center
601 Elmwood Avenue
Rochester, NY 14642-8668
Phone: (585) 276-5367

Co-Investigators:
Amy Harrington, MD
Rachel Flink-Bochacki, MD
Olivia Higgins, MD

1. PURPOSE OF THE STUDY AND BACKGROUND

1.1 Purpose of the study

The goal of this study is to determine if administering the anti-nausea medication ondansetron prior to doxycycline will decrease the rates of nausea and vomiting in patients taking doxycycline for antibiotic prophylaxis prior to undergoing surgical pregnancy termination.

1.2 Background

The use of prophylactic antibiotics are standard of care to prevent surgical site infections in gynecologic surgery[1]. Doxycycline is the recommended antibiotic of choice for surgical pregnancy termination and completion of spontaneous abortion given its effectiveness, low cost, and rare occurrence of allergic reaction[2]. Previous studies have shown that a common side effect of doxycycline is nausea and vomiting, with reported rates as high as 30-40%[3]. Nausea and vomiting may be reduced by taking the antibiotic with food[4]. Doxycycline given on an empty stomach the morning of a surgical pregnancy termination resulted in nausea and vomiting in 50% of patients and this rate was decreased to 15% when it was taken with food the night before surgery[5]. It is not known whether the use of scheduled prophylactic anti-emetics prior to doxycycline use would further reduce the rate of associated nausea and vomiting. The goal of our proposed study is to determine this.

Our study will be a double blinded randomized controlled trial that will examine whether the use of scheduled prophylactic anti-emetics prior to doxycycline use reduces the incidence of associated nausea and vomiting. Nausea and vomiting is distressing to patients and it affects their perioperative care. It is well documented that minor gynecologic procedures, such as uterine evacuations, can be performed safely with moderate and deep sedation without an endotracheal tube[6]. At our institution, patients experiencing nausea and vomiting prior to a surgical procedure receive

general anesthesia with endotracheal intubation, due to their symptoms, not because that would be the preferred route of anesthesia. For minor gynecologic procedures, the time for general anesthesia induction can be as long as the duration of the entire surgical procedure would be without general anesthesia. The use of general anesthesia increases the duration of time in the operating room, which increases the costs of operating room and anesthesia time, as well as recovery time for the patient[7]. General anesthesia also poses possible risks such as impairment of cardiovascular function and development of pneumonia[8,9].

In addition to anesthesia risks and patient discomfort, nausea and vomiting many also affect antibiotic efficacy due to reduced serum levels. Reeves' et al. showed lower serum doxycycline levels in patients with emesis within one hour of doxycycline administration. A serum level greater than 0.8 mg/L has been shown to provide adequate antibiotic prophylaxis. Vomiting after ingestion of doxycycline decreased serum levels by an average of 0.26 mg/L[5].

Reducing the rates of nausea and vomiting in patients undergoing minor gynecologic procedures may increase the efficacy of antibiotic prophylaxis, and decrease the rates of general anesthesia, patient risks and hospital costs. Most importantly, decreased nausea and vomiting will certainly improve patient experience and is clinically relevant because doxycycline is an antibiotic commonly used for many gynecologic procedures.

2. STUDY DESIGN

2.1 Overview

This will be a randomized controlled trial. Data will be collected by asking patients to fill out a demographic questionnaire and a baseline visual analog scale rating their nausea, pain and anxiety at their clinic appointment 1-2 days prior to their procedure. Patients will then take either ondansetron or a placebo 30 minutes prior to taking doxycycline the night before their procedure. They will then fill out a symptom/medication log recording their symptoms from the time that they take the study medication to the time that they present for their procedure. When they present for their procedure, patients will fill out a second identical visual analog scale rating nausea, pain and anxiety. The primary outcome is nausea and vomiting after taking the study drug and doxycycline the night prior to surgery. Doxycycline prophylaxis the night prior to surgery is the current standard of care. Eligible patients will be enrolled over the course of two years.

2.2 Rationale for Study Design

A randomized controlled trial was selected in order to study ondansetron's effect on the rates of nausea and vomiting in our particular population, so that patient's will not know if they are being given ondansetron or placebo before taking doxycycline. Some potential barriers that are expected in the study include that the patients may not fill out their symptom/medication log as this will be done at home. There are approximately 450 patients undergoing surgical termination of pregnancy at the

University of Rochester each year. In order to attain our goal sample size of 300 patients, we would have to enroll a large portion of the total patients. The primary hypothesis is that the rate of nausea and vomiting in patients undergoing surgical pregnancy termination will be decreased in the group receiving ondansetron versus the group receiving placebo.

3. CHARACERISTICS OF THE RESEARCH POPULATION

3.1 Subject Characteristics

3.1.1 **Number of Subjects:** 320 total subjects are expected to participate in the study. 160 total subjects will be randomized to receive ondansetron, while 160 total subjects will be randomized to receive placebo.

3.1.2 **Gender and Age of Subjects:** Patients included in the study will be pregnant females that are ages 18-45 years old.

3.1.3 **Racial and Ethnic Origin:** There will be no racial or ethnic restrictions to participation.

3.1.4 **Vulnerable Subjects:** The women included in this study will be pregnant, although the study interventions are surveys and the administration of a medication that is both safe in pregnancy and commonly used in pregnancy, ondansetron.

3.2 Inclusion and Exclusion Criteria

3.2.1 **Inclusion Criteria:**

- Pregnant women seeking care at the University of Rochester's Women's Health Practice Family Planning Clinic
- Ages 18-45 years old
- Undergoing second trimester surgical termination of pregnancy
- Proficient in reading, writing, and comprehending English
- Able to give informed consent

3.2.2 **Exclusion Criteria:**

- Less than 18 years old or older than 45 years old
- Not proficient in reading, writing, or comprehending English
- Not able to give informed consent
- Already taking antiemetics
- Doxycycline allergy
- Hyperemesis gravidarum
- History of gastroparesis or cyclical vomiting
- Unable to swallow pills

3.3 Discussion of Subject Population

Pregnant women ages 18-45 years old were selected for this study, as they will already be taking doxycycline as the standard of care when they present for abortion care.

4. SUBJECT IDENTIFICATION, RECRUITMENT AND CONSENT

4.1 Method of Subject Identification and Recruitment

Patients presenting for a surgical termination of pregnancy at Women's Health Practice will be offered the opportunity to participate in the study, after they have consented for a pregnancy termination. The investigators offering participation to patients would otherwise have routine contact with these patients, as they will be caring for them regardless of whether or not they participate in the study. If a subject is interested in participating, they will then be screened to determine if they are eligible. Patients will be assigned a random number for the study that will link together their demographic questionnaire, the two visual analog scales, their study drug, and their symptom/medication log.

4.2 Process of Consent

Patients will be consented by either Dr. Sarah Betstadt, Dr. Amy Harrington, the study coordinator, Rebecca Rowley, Dr. Ferdous Zannat, Dr. Mary Towner, Dr. Whitney Higgins or medical student Hannah Niebulski. The patients will be given a written consent form to sign that will be extensively reviewed with the individual consenting them. The written consents will be stored in a locked filing cabinet, and only the study coordinator, Dr. Sarah Betstadt or Dr. Amy Harrington will be able to access them.

5. METHODS AND STUDY PROCEDURES

Patients will be approached for participation in the randomized controlled trial after they have completed their pre-operative consultation and have already consented for pregnancy termination. Once patients are consented, they will be randomized to either the placebo or ondansetron group. The study medication will be taken 30 minutes prior to doxycycline medication the night prior to the pregnancy termination. Doxycycline prophylaxis is currently the standard of care, and is not part of the study procedure. Randomization scheme will be generated by computer generated random number blocks using a 1:1 ratio. Allocation will be done by sequentially numbered opaque sealed envelopes. The pharmacy will be compounding the study medication so that it looks exactly like the placebo tablet, in appearance, texture and smell. Once consented and randomized during their clinic visit 1-2 days before the procedure, patients will fill out a demographic questionnaire regarding their age, race, relationship status, income and education level, pregnancy history, gestational age, and symptoms of nausea and vomiting thus far in the pregnancy. This questionnaire will also include questions regarding cigarette and THC use, as well as any diagnoses of gastroesophageal reflux disease or hyperemesis gravidarum. They will then fill out a baseline visual analog scale rating their nausea, pain and anxiety, prior to leaving the office.

The study coordinator will also conduct a chart review for select information. For participants enrolled prior to this version date, it will be retrospectively collected. For participants after this protocol version date, it will be collected at the time of enrollment. They will collect Gestational Age at Procedure Date (weeks/days), Cervical Preparation (Miffepristone Y/N) (Misoprostol Y/N) (Cervical Dilators Y/N, IF Y, How Many?) Genetic Indication for Termination? (Y/N).

The patients will then be given a symptom/medication log to take home. The patients will use the log to record symptoms they experience from the time they take the ondansetron or placebo to the time that they present for their procedure. The log will include the timing of the study medication, doxycycline, whether the doxycycline was taken with food (and the time of/type of food if applicable), pain medications, and misoprostol. The log will also include the time of nausea and vomiting, and the severity of the nausea and pain (if applicable).

When patients present to the hospital for their procedure, the study coordinator, Dr. Olivia Higgins, Dr. Amy Harrington, or Dr. Sarah Betstadt will give them a second visual analog scale to fill out which asks them to rate their nausea, pain and anxiety. This scale will be identical to the one they filled out at their clinic visit. This scale will be filled out prior to their procedure. When the IV is placed for their procedure, a nurse will also draw a single 7 mL tube of blood; there are no additional needle sticks for this blood draw. The blood sample will later be tested for doxycycline serum levels.

5.1 Safety Assessments

A comprehensive medical history will be obtained at the patient's clinic visit, and a physical exam will be performed as well to ensure that patients are not only fit and able to undergo their procedure, but also to participate in the study.

5.2 Assessment of Subject Compliance

Compliance with the demographic questionnaire and baseline visual analog scale will be assessed by nature of them both being filled out and turned in at clinic. Compliance with taking the study medication will be assessed by asking the patient if and when they took either the ondansetron or placebo when they present for their procedure. Compliance with completing the symptom/medication log will be assessed by asking the patient to turn in their log when they present for their procedure. Compliance with the second visual analog scale will be ensured by asking the patient to complete it in the hospital before their procedure.

5.3 Data & Specimen Banking for Future Research Use

Blood samples that will be obtained from subjects on the morning of their procedure will be kept for future research use. The subjects have their blood drawn routinely the morning of their procedure as a standard of care in order to obtain a complete blood count and type and screen. Blood samples will be stored for the purpose of potentially comparing serum levels of doxycycline in the future. The samples will be stored in a secure location at the University of Rochester. the Study Coordinator, Dr. Sarah Betstadt, Dr. Amy Harrington and Dr. Olivia Higgins will have access to the samples. The samples will not be released to investigators outside the study team. The samples will be stored for 5 years and will be destroyed after that. The samples will be coded to allow subjects to be identified so as to potentially correlate their reported nausea/vomiting scales to serum levels of doxycycline. Subjects may withdraw the sample at any time should they choose to. They simply must contact the Study

Coordinatorto do so. Subjects will not be re-contacted regarding the banked samples.

5.4 Costs to the Subject

Subjects will not incur any additional costs by participating in this study.

5.5 Payment for Participation

Patients will not be reimbursed to participate in this study.

6. CONCOMITANT AND DISALLOWED MEDICATIONS

As per standard of care (and irrespective of the research study), in addition to doxycycline, patients will take 400 mcg of misoprostol bucally 3 hours before their procedure. It is also standard of care that patients are able to take either Ibuprofen or Tylenol #3 as needed for pain before their procedure. They will also be permitted to take any other medications that they take on a daily basis. None of these medications are part of the research protocol. They will be instructed not to take any antiemetics. We will record any medications that are used.

7. SUBJECT WITHDRAWALS

Patients will be withdrawn from the study if they themselves request to do so, or if they fail to take the study medication or the doxycycline. They will not be withdrawn if they fail to complete the demographic questionnaire, the baseline visual analog scale, the symptom/medication log, or the second visual analog scale. In the event that a patient does not complete one of these forms, The Study Coordinator will help her complete them. No additional study activities will be completed prior to subject withdrawal.

8. STUDY DRUG ADMINISTRATION/ASSIGNMENT

8.1 Study Drug

The study drugs include ondansetron and placebo. Neither of these drugs are investigational. The University of Rochester Investigational Drug Service will supply, package and label the study drugs. Each 8 mg ondansetron tablet contains ondansetron hydrochloride dehydrate equivalent to 8 mg of ondansetron. Each tablet also contains inactive ingredients lactose, microcrystalline cellulose, pregelatinized starch, hypromellose, magnesium stearate, titanium dioxide, triacetin, and iron oxide yellow[10].

8.2 Dosage of Study Drug

The dosage of ondansetron will be 8 mg, orally, once.

8.3 Subject Enrollment/Randomization

Subjects will be randomized to receive either ondansetron or placebo. They will be assigned via simple random allocation through the use of a computer software program that generates a random sequence.

8.4 Accountability of Investigational Supplies

The University of Rochester Pharmacy pharmacist will be responsible for receipt, storage, dispensing, collection, accountability and disposal of the investigational

drug. This includes maintaining accurate records of drugs received, used and returned. The pharmacist is the unblinded third party.

8.5 Subject Withdrawal of Study Drug

Subjects may stop study drug and still continue to be followed in the study.

8.6 Emergency Drug Disclosure

Drug disclosures will be maintained via envelopes. The Study Coordinator will receive and maintain this information. Disclosure of the subject's envelope should occur only in the case of a medical emergency. If such action is necessary, the pharmacist will reveal whether the subject received ondansetron or placebo, and this in turn will be revealed to the subject. Subjects will not be withdrawn from the study should drug disclosure occur.

9. SAFETY AND REPORTABLE EVENTS

9.1 Adverse Event Definition

An adverse event is any symptom, sign, illness, or experience which develops or worsens during the course of the study, whether or not the event is considered related to the study survey.

9.2 Serious Adverse Event

A serious adverse event is defined as any adverse medical experience that results in any of the following outcomes:

- death;
- is life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- requires medical or surgical intervention to prevent permanent impairment or damage.

9.3 Recording Adverse Events

At each subject visit the site study staff will assess adverse events by recording all voluntary complaints of the subject and by assessment of clinical and laboratory features. At each study visit, the subject should be questioned directly regarding the occurrence of any adverse experience since her last visit.

All adverse events, whether observed by the Investigator, elicited from or volunteered by the subject, should be documented. Each adverse event will include a brief description of the experience, the time of onset, the time of resolution, the duration and type of experience, the severity, the relationship to the study, contributing factors, and any action taken with respect to the study.

The recording of adverse events will take place from the time that the subject signs the consent until the subject completes the study (1-2 days after signing the consent) or withdraws from participation.

9.4 Responsibilities for Reporting Serious Adverse Events

All serious adverse experiences that occur during the study period will be recorded. The recording of experiences will occur from the time of signing of the consent until the subject completes the study or withdraws from participation.

10. RISK/BENEFIT ASSESSMENT

10.1 Risk Category:

Greater than minimal risk.

10.2 Potential Risks

Potential risks to subjects include the possibility of an adverse reaction to ondansetron (including headache, fatigue, malaise, constipation, drowsiness, sedation, dizziness, agitation, anxiety, paresthesia, sensation of cold, pruritus, skin rash, diarrhea, urinary retention, increased serum ALT, increased serum AST, hypoxia, and fever). Important or life-threatening side effects occurring in less than 1% of patients include abdominal pain, accommodation disturbance, atrial fibrillation, depression of ST segment on ECG, dyspnea, flushing, hepatic failure (when used with other hepatotoxic medications), hiccups, hypersensitivity reaction, hypokalemia, hypotension, liver enzyme disorder, mucosal tissue reaction, myocardial infarction, neuroleptic malignant syndrome, positive lymphocyte transformation test, prolonged Q-T interval on ECG (dose dependent), second-degree atrioventricular block, serotonin syndrome, Stevens-Johnson syndrome, supraventricular tachycardia, syncope, tachycardia, tonic-clonic seizures, torsades de pointes, transient blindness (lasted ≤48 hours), vascular occlusive events, ventricular premature contractions, ventricular tachycardia, and weakness[10]. There is also a potential risk of a patient's greater realization of the nausea and vomiting they are experiencing due to doxycycline. The use of doxycycline is already standard of care.

10.3 Protection Against Risks

The only additional risk may be loss of confidentiality. Study materials will be kept in a locked file cabinet.

10.4 Potential Benefits to Subjects

A potential benefit to subjects participating in this study is a decrease in their nausea and vomiting.

10.5 Alternatives to Participation

Patients who decline to participate in the study will receive the standard of care at our clinic for termination of pregnancy, which involves the use of doxycycline as a prophylactic antibiotic the night before the procedure, as well as misoprostol the morning of the procedure. They will also be able to take Ibuprofen or Tylenol #3 for pain. They will not fill out any surveys or logs or take the study drug.

11. CONFIDENTIALITY OF DATA AND INFORMATION STORAGE

11.1

Subject data will be identified in the research data set by random unique identifiable code.

The Study Coordinator will maintain the code to that information and it will be used to re-identify patients when they present for their procedure, in order to link together their demographic questionnaire, the two visual analog scales, their study medication, and the symptom/medication log. The research data will be secured in a locked filing cabinet during the study. No identifying information will be included in the research database except for the subject's ID number, any identifying information will be kept separately from the research database. Research files will be locked up when they are unsupervised, and only The Study Coordinator, Dr. Sarah Betstadt, or Dr. Amy Harrington will be able to access the files.

12. RESEARCH INFORMATION IN MEDICAL RECORDS

No research data will be included in the subject's medical record.

13. DATA ANALYSIS AND MONITORING

13.1 Sample Size Determination

Based on Reeves' study as well as anecdotal data from our clinic population, we expect vomiting to occur in approximately 30% of our patients who take their doxycycline the night before their procedure. To have 80% power to detect a 50% decrease in nausea and vomiting, we will need 122 patients in each arm of the study. In order to account for subject withdrawal or non-compliance, we intend to enroll 150 patients in each arm of the study. This will be a total of 300 subjects.

13.2 Planned Statistical Analysis

Our primary outcome of vomiting, will be analyzed using chi-square analysis. All dichotomous outcomes will be analyzed using chi-square analysis. Continuous variables will be examined using t-tests. If demographic variables are found to be confounders with significance, they will be placed into a logistic regression model. SPSS software will be used for statistical analysis.

14. REFERENCES

1. American College of Obstetricians and Gynecologists. Antibiotic prophylaxis for gynecologic procedures. ACOG Practice Bulletin No. 104. *Obstet Gynecol*. 2009;113:1180–9.

2. Sawaya GF, Grady D, Kerlikowske K, Grimes DA. Antibiotics at the time of induced abortion: the case for universal prophylaxis based on a meta-analysis. *Obstet Gynecol*. 1996;87(5 Pt 2):884–890.

3. Bryant SG, Fisher S, Kluge RM. Increased frequency of doxycycline side effects. *Pharmacotherapy*. 1987;7(4):125–129.

4. Risser W. Side effects of doxycycline in adolescents treated for pelvic inflammatory disease. *J Pediatr Adolesc Gynecol*. 2011;24(3):e87.

5. Reeves MF, Lohr PA, Hayes JL, Harwood BJ, Creinin MD. Doxycycline serum levels at the time of dilation and evacuation with two dosing regimens. *Contraception*. 2009;79(2):129–133.
6. Dean G, Jacobs AR, Goldstein RC, Gevirtz CM, Paul ME. The safety of deep sedation without intubation for abortion in the outpatient setting. *Journal of Clinical Anesthesia*. 2011;23(6):437–442.
7. Brooks DM, Hand WR. A cost analysis: general endotracheal versus regional versus monitored anesthesia care. *Mil Med*. 1999;164(4):303–305.
8. American Society of Anesthesiologists (ASA). Continuum of Depth of Sedation Definition of General Anesthesia and Levels of Sedation/Analgesia. 2004. Available at: https://www.asahq.org/For-Members/Standards-Guidelines-and-Statements.aspx. Accessed August 10, 2014.
9. Jenkins K, Baker AB. Consent and anaesthetic risk. Anaesthesia. 2003;58(10):962–984.
10. GlaxoSmithKline. Zofran (ondansetron) prescribing information. 2014. Available at: https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Zofran_Oral/pdf/ZOFRAN-ORAL.PDF. Accessed April 14, 2015.