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Official Study Title: Rectal Misoprostol as a Hemostatic Agent During Abdominal Myomectomy

NCT number: NCT03064568

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Unique Protocol ID: HSC20150554H

Item 1 UTHSCSA Tracking Number	HSC20150554H: Title: Rectal Misoprostol as a Hemostatic Agent During Abdominal Myomectomy

Item 2 Abstract / Project Summary	Provide a succinct and accurate description of the proposed research. State the purpose/aims. Describe concisely the research design and methods for achieving the stated goals. This section should be understandable to all members of the IRB, scientific and non-scientific. **DO NOT EXCEED THE SPACE PROVIDED**.

Purpose/Objectives: Determine if rectal misoprostol decreases bleeding during abdominal myomectomy

Research Design/Plan: Enroll women undergoing abdominal myomectomy to either receive preoperative rectal misoprostol or an inert tablet and determine if there is a significant difference in blood loss, need for transfusion, decrease in postoperative hemoglobin and hematocrit, postoperative pain, and side-effects from medications.

Methods: Prospective double-blinded study completed at a tertiary care center. We plan to enroll 75 participants and monitor pre-operative, intra-operative, and post-operative variables to determine if there is a significant difference in any of the above measures.

Clinical Relevance: To determine if pre-operative rectal misoprostol administration decreases blood loss and need for transfusion in women undergoing abdominal myomectomy.

Item 3 Background	
Describe past experimental and/or clinical findings leading to the formulation of your study. *For research involving unapproved drugs, describe animal and human studies.* *For research that involves approved drugs or devices, describe the FDA approved uses of this drug/device in relation to your protocol.*	Uterine fibroids are very common, affecting up to 70% of Caucasian women and 80% of African-American women by age 50 in the United States[1]. When symptomatic, they can cause symptoms including abnormal uterine bleeding, pressure-like pain, infertility, and recurrent pregnancy loss, and often surgical intervention is indicated[2]. Many methods have been described for decreasing blood loss during myomectomy including intramyometrial vasopressin[3], intravenous oxytocin[4], tourniquets[5], intramyomal bupivacaine plus epinephrine[6], morcellation[7], rectal misoprostol[8], and uterine artery ligation[9]. At our institution, the injection of vasopressin near the myoma is commonly used to decrease the amount of bleeding during the procedure[3]. Recently an article was published by Frederick et al that examined the use of misoprostol and perivascular vasopressin versus vasopressin alone and found a significant decrease in the amount of bleeding[8]. Vasopressin in that study was administered in a way that is different compared to our usual practice, but the novel concept was the addition of preoperative misoprostol. Misoprostol is FDA-approved for prevention of NSAID-induced gastric ulcers, but has been used extensively in obstetrics and gynecology to cause cervical ripening, to induce or augment uterine contractions, and treatment of postpartum hemorrhage due to atony. It has also been reported in other studies to decrease uterine bleeding when administered prior to myomectomy[10-12]. Our objective is to determine if it contributes to decreased blood loss when combined with local vasopressin. We have based our sample size calculation on the study done by Frederick et al to find a minimum difference of 1.4 with a p-value of 0.5[8]. **1.** Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. *Am J Obstet Gynecol.* Jan 2003;188(1):100-107. **2.** Buttram VC, Reiter RC. Uterine leiomyomata: etiology, symptomatology, and management. *Fertil Steril.* Oct 1981;36(4):433-445. **3.** Frederick J, Fletcher H, Simeon D, Mullings A, Hardie M. Intramyometrial vasopressin as a haemostatic agent during myomectomy. *Br J Obstet Gynaecol.* May 1994;101(5):435-437. **4.** Agostini A, Ronda I, Franchi F, et al. Oxytocin during myomectomy: a randomized study. *Eur J Obstet Gynecol Reprod Biol.* Feb 2005;118(2):235-238.

	5. Kathiresan AS, Brookfield KF, Gonzalez-Quintero VH, Verma U. Vasopressin versus a combination of vasopressin and tourniquets: a comparison of blood loss in patients undergoing abdominal myomectomies. *Aust N Z J Obstet Gynaecol.* Feb 2011;51(1):79-83. **6.** Zullo F, Palomba S, Corea D, et al. Bupivacaine plus epinephrine for laparoscopic myomectomy: a randomized placebo-controlled trial. *Obstet Gynecol.* Aug 2004;104(2):243-249. **7.** Chen C. Laparoscopic myomectomy for large myomas. *Int Surg.* 2006 Sep-Oct 2006;91(5 Suppl):S77-80. **8.** Frederick S, Frederick J, Fletcher H, Reid M, Hardie M, Gardner W. A trial comparing the use of rectal misoprostol plus perivascular vasopressin with perivascular vasopressin alone to decrease myometrial bleeding at the time of abdominal myomectomy. *Fertil Steril.* Oct 2013;100(4):1044-1049. **9.** Sinha R, Sundaram M, Mahajan C, Raje S, Kadam P, Rao G. Laparoscopic myomectomy with uterine artery ligation: review article and comparative analysis. *J Gynecol Endosc Surg.* Jan 2011;2(1):3-10. **10.** Celik H, Sapmaz E. Use of a single preoperative dose of misoprostol is efficacious for patients who undergo abdominal myomectomy. *Fertil Steril.* May 2003;79(5):1207-1210. **11.** Kongnyuy EJ, Wiysonge CS. Interventions to reduce haemorrhage during myomectomy for fibroids. *Cochrane Database Syst Rev.* 2014;8:CD005355. **12.** Ragab A, Khaiary M, Badawy A. The Use of Single Versus Double Dose of Intra-vaginal Prostaglandin E2 "Misoprostol" prior to Abdominal Myomectomy: A Randomized Controlled Clinical Trial. *J Reprod Infertil.* Jul 2014;15(3):152-156.
Item 4 Purpose and rationale *Insert purpose, objectives and research questions/hypotheses here.* *If you cut and paste from another document, make sure the excerpted material answers the question*	Insert purpose: Purpose is to identify if misoprostol in addition to local vasopressin decreases blood loss when compared to vasopressin alone, which is our current practice at this time. The study will be double-blinded with neither the patient nor the researcher knowing whether the placebo or the misoprostol was given. We will monitor patients for decrease in hemoglobin and hematocrit, need for transfusion, and operative time among other measures of perioperative morbidity to see if the addition of misoprostol makes a significant difference. We will also observe patients to see if there are any side effects of misoprostol that make its use undesirable.

Item 5 Study Population(s) Being Recruited In your recruitment plan, how many different populations of prospective subjects do you plan to target? Provide number: 1	Identify the criteria for **inclusion**:	Identify the criteria for **exclusion**:
e.g., a population can be individuals with type 2 diabetes controlled with diet and/or a population of healthy controls. Or a population can be individuals attending an education program, etc. <u>List each different population</u> on a separate row and provide a short descriptive **label**: *(e.g., normal-healthy, diabetics, parents, children, etc.)* *To add rows use copy & paste*		
Normal-healthy adult female	Female age 20-50 y/o who plan to undergo abdominal myomectomy for symptomatic myomatous uterus, single attending surgeon to perform case to keep other factors equivalent.	Patient with contraindication to misoprostol or vasopressin, personal history or cardiac or pulmonary disease, history of prior myomectomy

Item 6
Research Plan / Description of the Research Methods ***a.*** *Provide a* ***comprehensive narrative*** *describing the* ***research methods****.*
Provide the ***plan for data analysis*** *(include as applicable the* ***sample size calculation).***

Step-by-Step Methods: We plan to recruit study participants from women who presented for surgical management of myomatous uterus at UTHSCSA MARC clinic and University Downtown REI clinic and who plan to undergo abdominal myomectomy. These women all undergo full history and physical exam including transvaginal sono per standard care. All women with planned myomectomy receive Depo Leupron prior to surgery per standard care and undergo routine pre-operative laboratory testing including hemoglobin and hematocrit. If enrolled in the study, patients will be consented at their pre-op appointment for the study and be asked to complete a visual analog scale to assess pre-operative pain. Patients will be randomized to receive misoprostol 800mcg per rectum or an inert tablet(s) per rectum 30 minutes preoperatively. Since initiation of this research study, the shape of misoprostol has changed. The Investigator and his associates have made multiple attempts and have reached out to multiple pharmacies to identify a new vendor for a placebo that has the same color and shape as the misoprostol. Unfortunately, we have been unable to find a placebo that is similar to the drug. Given this new obstacle we pose that a physician or REI fellow will assist as part of this research. The third-party physician will administer the misoprostol/ or placebo rectally as dictated by the protocol. The PI and all those associated with this research during the procedure will turn their backs and not have view of the medication that is administered. This will maintain blinding. This will not pose any additional risks for the patient, and blinding will be maintained. Randomization will be performed by a third party (FORU) so that neither the surgeon nor patient will know which intervention was performed, and interventions will be placed in sealed, sequentially numbered, opaque envelopes. Researcher team will have all needed data corresponding with randomized code which will be broken at conclusion of study and will be able to match code with patient's initials and MRN after study completion to analyze data. Myomectomy will then be performed per standard care with the use of local vasopressin to aid in decreasing blood loss per our normal standard of care. Length of skin incision, surgical time, enucleation time, number of uterine incisions, number of myomas, size of myomas, weight of myomas, estimated blood loss, need for transfusion, and complications will be recorded. Estimated blood loss will be calculated by the addition of the blood in the aspiration canister combined with the estimated blood on lap sponges. Postoperatively, patients will be monitored 24 hours post-op in the hospital for febrile morbidity and need for transfusion; they will also undergo repeat hemoglobin and hematocrit measurement 24 hours postoperatively. Patient pain will be assessed with the visual analog scale prior to discharge from hospital. All patients will also be asked about any associated side-effects of misoprostol prior to discharge including fever, chills, and/or diarrhea.

Data Analysis Plan: Differences in categorical variables will be calculated using the chi-square or Fisher's exact t-test. Continuous variable will be analyzed using independent t-test.

Sample size/power calculation:

Equation 1: Sample size for a comparison of two means.

$$N = \frac{4\sigma^2(z_{crit} + z_{pwr})^2}{D^2}$$

Input Values		**Calculated Results**		
Minimum expected difference:	1.4	Sample size (N):	64.07248766090572	(total, 2 group
Estimated standard deviation:	2.0	Z_{crit}:	1.959963986120195	
Desired power:	0.80	Z_{pwr}:	0.8416212327266186	
Significance criterion (2-tailed):	0.05			

Item 7 Risks Section:

Complete the following table to describe the risks of all **research procedures** listed in Step 2, Institutional Form (items 28-34). *Do not list risks of Routine care procedures here.*

☒ N/A, Risks are described in the informed consent document – do not complete this table.

Research procedures	**Risks**
example: • History and physical • Questionnaire • Laboratory tests *Add or delete rows as needed*	List the reasonably expected risks under the following categories as appropriate: