RESEARCH STUDY PROTOCOL

Bowel Function After Minimally Invasive Hysterectomy: A Randomized Controlled Trial
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Title: Bowel Function After Minimally Invasive Hysterectomy: A Randomized Controlled Trial

Abbreviated Title: Bowel Function/PEG study

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ABSTRACT
Postoperative constipation affects up to a third of women undergoing minimally invasive (MIS) gynecologic surgery and is a major source of anxiety and discomfort. The average time to first bowel movement after gynecologic surgery is about 2 to 4 days and some factors responsible for this include anesthesia inhibitory effect on gastrointestinal motility, opioid pain medication use, chronic NSAID use and anatomic manipulation[1].

There are no established regimens to manage postoperative constipation after minimally invasive gynecologic surgery. A few post-operative regimens have been investigated with mixed results. One such study evaluating the implementation of postoperative bowel regimen with polyethylene glycol (PEG) vs. Docusate found no significant impact on postoperative bowel function while another found improved constipation with use of Docusate and Senna vs. placebo. [1, 2]. There have been no studies looking at the effect of preoperative bowel regimens on postoperative bowel function.

The purpose of this study is to evaluate postoperative bowel function after minimally invasive hysterectomy in women receiving a preoperative 10-day bowel regimen of PEG daily.

1.0 STUDY PURPOSE AND RATIONALE

Hysterectomy is one of the most commonly performed surgeries in the United States. Many of the underlying conditions prompting hysterectomy such as uterine fibroids, pelvic organ prolapse, endometriosis and cancer contribute to baseline constipation. Nineteen percent of hysterectomy patients and 27% of patients undergoing prolapse on urinary incontinence surgery have baseline constipation [3]. Additionally, patients undergoing pelvic surgery are at increased risk of constipation post-operatively due to anesthesia, bowel manipulation, inactivity and narcotic use [4-6]. A study reported that 13.7% of urogynecology patients called the office post operatively with concerns related to constipation[7]. A similar study looking at post-operative complaints in a general gynecology population found that 34% of patients reported constipation symptoms after discharge [8]. In addition to the bloating and discomfort caused by constipation, avoidance of straining with defecation may help prevent the development or recurrence of pelvic organ prolapse [9, 10]. Decreasing abdominal straining could also help prevent vaginal cuff dehiscence [11, 12]

Postoperative docusate is commonly used after gynecologic surgery to prevent constipation, though little evidence exists to support this practice. Several postoperative regimens have been investigated but no clearly superior regimen has been identified. In urogynecology patients, docusate plus Senna was found to improve constipation and time to first bowel movement when compared with placebo [13]. However, Polyethylene glycol vs. Docusate did not show improvement in constipation symptoms or time to first bowel movement [14, 15]. In the Orthopedic literature, Lubiprostone was found to be equivalent to Senna [16].

Given the high rate of baseline constipation and postoperative constipation in patients undergoing hysterectomy, and the unsatisfactory results with postoperative bowel regimens, we hypothesize that improving baseline constipation may help improve postoperative patient outcomes. For patients undergoing cardiac surgery, preoperative constipation was found to significantly predict post-operative constipation rates [17].

Polyethylene glycol is an osmotic laxative that has been shown to be safe, effective and well tolerated for the treatment of both acute and chronic constipation [18]. It is readily available over the counter and has been shown to be safe for long-term use. The goal of this study is to assess the effect of preoperative administration of Polyethylene glycol on postoperative constipation symptoms and constipation related quality of life.

2.0 STUDY DESIGN AND STATISTICAL PROCEDURES

2.1 Overall design

Type of study: A randomized controlled trial

Randomization: Block randomization by surgical subspecialty- division of minimally invasive gynecologic surgery, division of urogynecology, division of gynecologic oncology

Single vs. multi-center: Single center

2.2 Study objectives

2.2.1 Primary objective: To compare postoperative constipation as measured using PAC-QOL & PAC-SYM questionnaires in women receiving a 10-day preoperative bowel regimen versus those receiving standard preoperative care (no intervention)

2.2.2 Secondary objectives:

a) To compare postoperative abdominopelvic pain as measured on a VAS pain scale in women receiving a 10-day preoperative bowel regimen versus those receiving standard preoperative care (no intervention)

b) To compare postoperative narcotic use in women receiving a 10-day preoperative bowel regimen versus those receiving standard preoperative care (no intervention)

2.3 Aims & Hypotheses

2.3a Specific Aim 1

To determine if there is a difference in postoperative constipation between women receiving a 10-day preoperative bowel regimen and those receiving standard preoperative care (no intervention)

2.3a.1 Hypothesis 1

Postoperative constipation is decreased in women receiving a 10-day preoperative bowel regimen versus those receiving standard preoperative care (no intervention)

2.3b Specific Aim 2

To determine if postoperative pain as measured on a VAS pain scale differs between women receiving a 10-day preoperative bowel regimen and those receiving standard preoperative care (no intervention)

2.3b.1 Hypothesis 2

Postoperative pain is improved in women receiving a 10-day preoperative bowel regimen versus those receiving standard preoperative care (no intervention)

2.3c Specific Aim 3

To determine if postoperative narcotic use differs between women receiving a 10-day preoperative bowel regimen and those receiving standard preoperative care (no intervention)

2.3c.1 Hypothesis 3

Postoperative narcotic use is decreased in women receiving a 10-day preoperative bowel regimen versus those receiving standard preoperative care (no intervention)

2.4 Data Management and Analysis

In this study, the primary objective is to analyze the effect of 10-day preoperative bowel regimen on postoperative constipation as measured on PAC-QOL and PAC-SYM validated questionnaire

Justification of sample size: For the PAC-SYS questionnaire the minimal important difference in the score is estimated to be 0.5 [19, 20]. Using the PAC-SYS score data from Edenfield et al [15] and Marciniak et. al [16]. We estimate that in order to detect a score difference of 0.5 on the PAC-SYS score with 80% power and a two-sided alpha of 0.05 that we would require 78 subjects evenly divided into two groups. Assuming that there is a 20% drop out rate we plan to enroll 98 subjects for the main part of the study.

We would like to do a small piolet of 3 patients to confirm that we are able to smoothly conduct the study. These 3 will be excluded from the final analysis.

A total of 101 subjects will be enrolled.

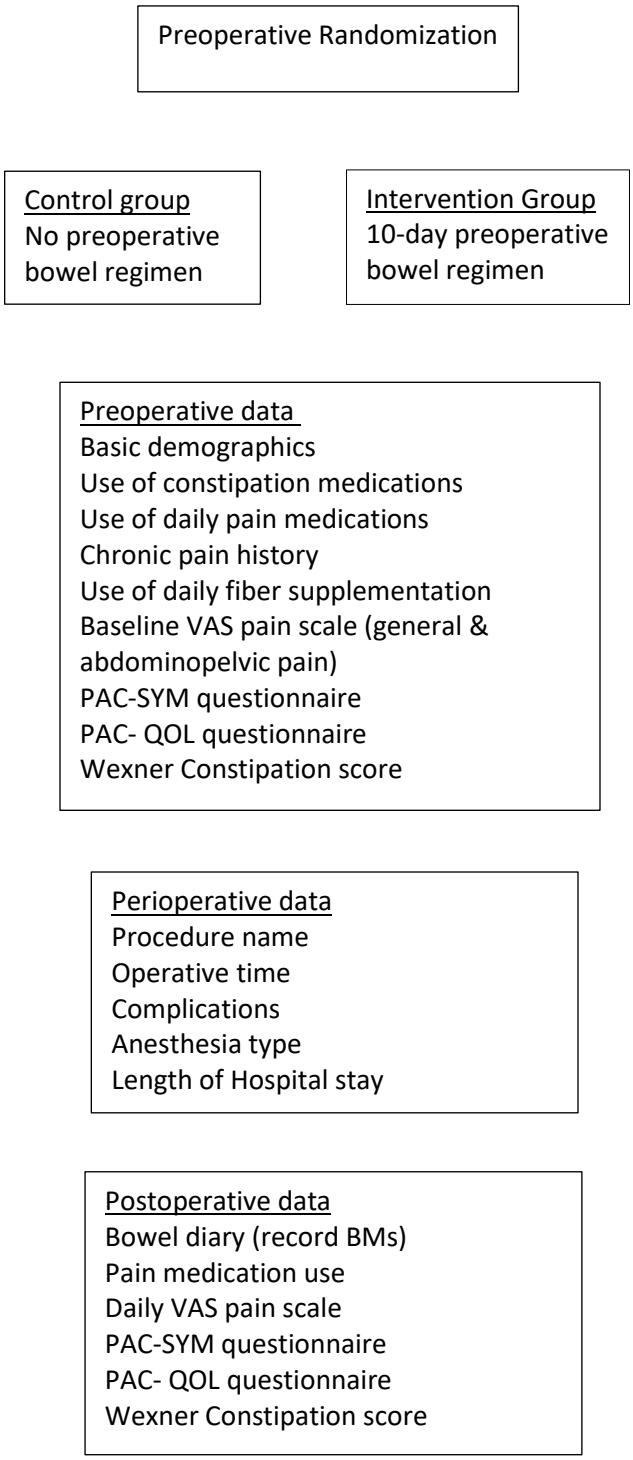
General Analyses

Continuous variables will be summarized using means, standard deviations, medians, and ranges. If normally distributed, they will be analyzed using parametric tests such as T-test and analysis of variance. To find associations between continuous variables and to control by relevant covariates we will use multiple regressions. If the normality assumption is violated we will use non-parametric tests such as Mann-Whitney or Kruskal-Wallis.

Categorical variables will be summarized with frequencies and percentages and analyzed with logistic regression or categorical response models. 95% confidence intervals will be provided for descriptive statistics, as warranted. Subject characteristics are assumed to be comparable at the start of the study (randomization design) and so no formal statistical group comparisons will be conducted on the subject characteristics.

An overall alpha-level of 0.05 will be used as a cut-point for statistical significance and all statistical tests will be two-sided. All data will be analyzed by the University of Chicago Medicine Biostatistics team.

2.5 Graphical schema of study



3.0 STUDY PROCEDURES

- For the piolet first 3 subjects they will be assigned to the treatment arm. For the remaining 98 subjects, after informed consent is obtained subjects will be randomized via sealed, opaque envelopes containing a sub-specialty block scheme to one of the two groups:
    - Control Group: Standard preoperative care (no preoperative bowel regimen)
    - Intervention Group: Preoperative bowel regimen (PEG 3350)

- Subjects in the intervention group will be given the PEG 3350 (10-day supply) to use for the 10 days prior to surgery.
- Preoperative data will be obtained from all subjects: basic demographics, use of constipation medications, use of daily pain medications, chronic pain history, use of daily fiber supplementation, baseline VAS pain scale (general & abdominopelvic pain).
- Preoperatively, all subjects will be requested to complete the following questionnaires: Wexner Constipation Score Questionnaire, validated PAC-SYM questionnaire, and PAC- QOL questionnaire
- Perioperative data obtained will include procedure name, operative time, complications, anesthesia type, length of Hospital stay
- Post operatively, all subjects will be requested to complete a bowel diary (record BMs), record pain medication use, report daily VAS pain scale, complete PAC-SYM questionnaire, PAC-QOL questionnaire and Wexner Constipation Score Questionnaire

4.0 STUDY DRUGS

MiraLAX, Polyethylene Glycol 3350 is an FDA approved over-the-counter osmotic laxative. It works by attracting water in the colon to ease, hydrate and soften stool. MiraLAX relieves constipation without gas, bloating, cramping or sudden urgency. In multiple clinical trials, MiraLAX has been proven to result in a BM within 24 to 72 hours. MiraLAX is formulated as a powder. 1 packet of powder (17g) is stirred and dissolved in 4 to 8 oz. beverage; to be used daily for at least 7 days.

5.0 STUDY INSTRUMENTS: Questionnaires (See Appendix)

6.0 STUDY SUBJECTS

- Any woman ≥ 18 years of age undergoing a a minimally invasive hysterectomy (Laparoscopic, robotic, transvaginal)

6.1 Inclusion criteria:

- Any woman ≥ 18 years of age undergoing a minimally invasive hysterectomy (Laparoscopic, robotic, transvaginal)
- Able to understand the consenting process and willing to participate in study

6.2 Exclusion criteria:

- Planned laparotomy
- Emergent surgery
- Regular preoperative use of PEG 3350, laxatives, enemas or suppositories
- Planned bowel surgery
- Presence of colostomy
- Inability to consent
- Medical problems as follows:
    - CKD (Cr: > 1.2 mg/dL)
    - IDDM
    - Cardiac disease

- Gastric ulcers
- Difficulty swallowing or esophageal stricture
- Persistent nausea or vomiting
- Signs or symptoms of a small bowel obstruction

7.0 RECRUITMENT

Benign gynecology, urogynecology or gynecologic oncology surgeons who perform minimally invasive hysterectomy will be asked for their permission to consider their patients for the study.

A member of the research team will search the University of Chicago operating room schedules of the participating providers to identify potential study participants scheduled to undergo a minimally invasive hysterectomy. Data from the medical record system will be used to evaluate inclusion criteria.

Once a subject has been identified, the research team will contact the operating surgeon via encrypted email for permission to contact the specific potential subject for study participation.

A member of the research team will contact the potential subject offer them participation in the study and confirm participation criteria. Once a patient is identified as a potential study participant, the informed consent process will be completed as detailed in the 'Informed Consent Process' section.

Please see informed consent section for further discussion of why in person recruitment and consent is not planned.

8.0 INFORMED CONSENT PROCESS

After a member of the research staff determines eligibility of study participants, the informed consent process will be completed in three possible ways as listed/explained below by the PI or research staff (Co-investigator or other delegated study staff):

Option 1: (in person consent)

- Subject will be offered an in person visit with a member of the research staff.
- During this visit, the informed consent and HIPAA form will be explained and all questions answered
- The informed consent and HIPAA form will be signed by the patient and a copy given to them for their personal records
- The original 'wet-ink' signed consent and HIPAA form will be stored in a locked cabinet in the research coordinator's office.
- After consent, patient will be randomized and preoperative medication will be provided based on randomization group
- All preoperative data as previously outlined will be obtained

Option 2: (phone discussion with paper consent form)

- The Subject will be offered a phone discussion. Prior to this phone discussion a copy of the consent form will be mailed to the subject. Receipt of consent will be verified before the phone consenting process begins.
- During this conversation the informed consent and HIPAA form will be explained and all questions answered
- Two copies of the consent and a stamped, addressed envelope will be mailed to the patient to sign and return the consent form.
- After receipt of the consent the patient will be randomized and the subject will be randomized and the study medications and/or materials will be mailed to the subject.

Option 3: (phone discussion with electronic consent form)

- The Subject will be offered a phone discussion. Prior to this phone discussion an email with a link / instructions for accessing REDCap will be sent to the subject. They will be instructed to access the electronic form in order to review it during the consenting process.
- During this conversation the informed consent and HIPAA form will be explained and all questions answered
- The patient will sign the electronic consent form accessed through REDCap.
- Once the consent for is completed electronically the form will be printed and kept in a locked filling cabinet for our records.
- The subject will be randomized and a copy of the signed consent form and the study medications and/or materials will be mailed to the subject.

For all options, participants will have access to the consent form prior to and during the consenting process. In addition, when participation is offered to the patient, the informed consent and HIPAA form will be explained in detail along with the study design, procedures, inclusion/exclusion criteria, risks and benefits, and study requirement. It will be emphasized that participation is completely voluntary and that she may revoke her participation at any time. There will be no further documentation of the informed consent process.

We recognize that in person consents are preferable. The above recruiting and consent process is being proposed for the following reasons:

1) Patients undergoing minimally invasive hysterectomy will often have only one visit with the surgeon prior to surgery. During this visit a full history and physical is taken and surgical consent is performed. Attempting to perform study consent at this visit is not optimal for the following reasons
   a. It is likely that potential subjects will not be offered enrollment in the study because of time constraints.
   b. Consenting for this study on in addition to consent for surgery could be overwhelming for subjects and limit their ability to give a truly informed consent. A phone conversation at a later time would allow for the patient to have more time with the research staff and less to digest in one sitting.

2) Hysterectomy patients often have preoperative visits that are several months before their surgery. We would like consent patients for this study closer to the time they will be participating in the study.

3) Gynecology sees outpatients at DCAM as well as a number of UCM facilities around southland Chicago. The off campus patients have a different socioeconomic and racial makeup and thus, should be included. Without phone recruiting and phone consent options off campus locations will have very limited participation for the following reasons
   a. Unless the treating provider is part of the research team, research staff is not available at off campus locations.
   b. Many of these patients live far from campus and will not be willing/able to come in for a dedicated study visit with our research staff. This would disproportionately impact patients who do not drive because of age or socioeconomic status.

We feel that offering consent at a time separate from surgical consent is most respectful of our subjects and will allow for true informed consent. Offering a telephone option for consent will minimize the burden placed on subjects and be most inclusive. In person consent will also be offered to patients who prefer this.

We additionally feel that offering an electronic consent will limit the burden placed on patients. It will limit the number of things that they need to receive in the mail and mail back to us.

9.0 CONFIDENTIALITY OF STUDY DATA

To ensure confidentiality of medical information, each patient will be assigned a unique identifier in the database that can be linked to the medical record number. The database will be password-protected, encrypted and stored on a secure server accessible only from computers in the OBGYN department. Subject demographics and date will be entered into REDCap (system 4283). REDCap is a mature and secure web application for building and managing online surveys and databases. It allows data to be exported to Excel and SPSS.

REDCap has the capacity for allowing patients to securely link to questionnaires and consent forms. The electronic consent form will be accessed via an email link. Our team has consulted with Julissa Acevedo who is in charge of REDCap for CRI. She agrees that REDCap is HIPPA compliant and data is encrypted during transmission, allowing for data collection out-of-network, off-campus, remotely, etc. Patients are able to sign the consent for with the use of a mouse or a touch screen.

10.0 PRIVACY PROTECTIONS

The Principal Investigator and study staff will assure that the subject's privacy will be strictly maintained and that their identities are protected from unauthorized parties. This will be accomplished by securing all study documents and subject information. These files will be accessible to study staff only and maintained in a secure study office. The study staff will assign a code (numbers and/or letters) to the subject for data analysis. Documents that contain identifiers will be kept in a locked research office and/or stored within computers with password protection and encryption. We will safeguard patients' expectation that the information they offer will be held in confidence. We will protect each participant's information as prescribed by the University and Hospital police and relevant Federal law.

11.0 POTENTIAL RISKS

There is minimal additional risk to the subjects in the intervention group. Miralax is an FDA approved medication for treatment and prevention of constipation. This medication has mild side effects, which may include loose watery or frequent stools. The patients' privacy will be protected with the highest level of security however, potential for breaches in security must always be considered.

12.0 DATA AND SAFETY MONITORING

Study documents and subject information will be collected in files designed specifically for the study. These files will be accessible to study staff only and maintained in a locked and secure research study office. Electronic data will be stored in a mature and secure web application for building and managing online surveys and databases. To ensure confidentiality of medical information, each patient will be assigned a unique identifier in the database that could be linked to the medical record number. The database will be password-protected, encrypted and stored on a secure server accessible only from computers in the OBGYN Division. For data analysis, all stored data will be exported to Excel and SPSS.

13.0 POTENTIAL BENEFITS

Patients in the intervention arm may experience improvement in postoperative constipation. There are otherwise no additional potential benefits to participants of this study.

14.0 ALTERNATIVES

The alternative to this study is not to participate

15.0 RESEARCH AT EXTERNAL SITES

Not Applicable

16.0 UNIVERSITYOF CHICAGO AS LEAD INSTITUTION

This is a single center study, with recruitment from University of Chicago Medical Center and a few satellite sites: Locations: The study patients will be recruited from outpatient settings of University of Chicago Medical Center:

University of Chicago DCAM - 5758 S. Maryland Ave Chicago, IL 60637

University of Chicago South Loop - 1101 S. Canal St. Suites 201 & 202 Chicago, IL 60607

University of Chicago Orland Park - 14290 S. La Grange Rd. Orland Park, IL 60462

University of Chicago Harvey: 71 W. 156th St. Harvey, IL 60426

University of Chicago Schererville: 222 Indianapolis Blvd. Schererville, IN 46375

University of Chicago Streeterville : 680 N. Lake Shore Dr.Suite 117, Chicago, IL 60611

University of Chicago Flossmoor: 19550 Governors Hwy. Flossmoor, IL 60422

Proposed Timeline

Overall timelines: (1.5)
Date of initiation of study: 5/1/2019
Date of study enrollment completion: 11/1/2020
Follow up of last patient: 11/10/2020
Date of completion of analysis and submission of publication: 2/1/2021

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