

MMC 2015-63 Belladonna and Opium rectal suppository effect on postoperative pain and nausea following Total Laparoscopic and Robot-Assisted Hysterectomy.

01/18/2017

B&O for TLH Post-operative Pain and Nausea Study Protocol

This study is a single-center, double-blind, randomized placebo-controlled trial to assess the impact of immediate postoperative Belladonna and Opium rectal suppository use on postoperative pain and nausea following total laparoscopic and robot-assisted hysterectomy. Study activities to take place at Mercy Medical Center, involving both outpatient and inpatient surgical settings. The duration of the trial will be 12 months, with a goal of enrolling 130 patients during this time period. Patients eligible for trial participation are women between ages 18 and 75 undergoing level I total laparoscopic or robot-assisted hysterectomy with or without bilateral salpingo-oophorectomy, with or without cystoscopy performed post-procedure, with or without lysis of adhesions, and with or without surgical treatment of endometriosis, with no additional surgical procedures being performed (i.e. no lymph node dissection or urogynecologic suspension or sling procedures). Patients will be excluded from the study if they have contraindications to the use of B&O suppositories: these contraindications are glaucoma, severe hepatic or renal disease, bronchial asthma, history of narcotic idiosyncracies, respiratory depression, convulsive disorders, acute alcoholism or delirium tremens, or regular use of an anticholinergic medication (twice per week or more frequently). Patients will be withdrawn from the study if the original planned surgery is not performed. If the original planned study is not performed, a suppository will not be placed following surgery. Patients may also opt to withdraw from the study, or may be withdrawn from the study if there is a failure of the research team to adhere to the study protocol. There will be no financial incentives offered for trial participation.

Only the patients of clinical investigators from this trial will be considered for participation in this study. Clinical investigators posting patients for total laparoscopic or robotic hysterectomy at Mercy Medical Center will inform patients of the presence of the clinical trial at the time of surgical posting, using an IRB-approved script (appendix A). The chart number of patients posted for total laparoscopic or robot-assisted hysterectomy will be forwarded to the co-investigator by the clinic surgical coordinator at the time of surgical posting. The co-investigator will review each chart and conduct a telephone interview with each patient prior to surgery to verify trial eligibility and to answer any questions about the trial. Patients will be made aware that study participation is voluntary, and that if they chose to not participate, they will receive standard postoperative pain and nausea pharmacologic management. On the day of surgery, a member of the research team will meet with the patient pre-operatively in a private pre-operative holding area to review and sign a written consent for participation in the trial (Appendix B). This member of the research team would be familiar with the study protocol and risks of the pharmacologic intervention under investigation. These steps will allow patients to be fully informed, and will ensure patient safety and support during the short interval of the study.

On the day of surgery, patients will be randomized to either B&O rectal suppository or to a placebo of glycerin rectal suppository. This study employs a glycerin rectal suppository as a placebo because this over-the-counter medication has limited effects, similar to those of a Belladonna & Opium Suppette, and is similar in size, physical appearance and mechanical properties to a Belladonna & Opium Suppette. A placebo-free comparison group will not be used, as this would change the study design from a double-blind clinical trial to a single-blind clinical trial, with greater potential for investigator bias to influence study results. Additionally,

it is not thought that results for a placebo-free comparison group would substantially differ from those of a glycerin suppository placebo group, and would require a larger study population and greater study resources to achieve findings of similar significance and power. Randomization is to be performed by a biostatistician, with a sealed envelope to be created for each patient containing information regarding randomization to either placebo or intervention group. In the operating room, this envelope will be opened, and the circulating nurse would draw the indicated medication from the Pyxis system. Drug dictionary entries will be created within the Pyxis system by the Mercy Medical Center Department of Pharmacy, so that the Belladonna & Opium Suppette #16A (16.2mg / 60mg), and the glycerin suppository are represented as “Protocol Drug #1” and “Protocol Drug #2”. The patient’s electronic medical record will reflect that “Protocol Drug #1” or “Protocol Drug #2” was received by the patient, so that the nurses caring for the patient postoperatively will be blinded as to which suppository the patient received.

A suppository will be placed rectally by a member of the surgical team at the conclusion of surgery, prior to departure from the OR and awakening from anesthesia. Post-operative placement was selected to minimize interaction with intraoperative anesthetic and analgesic medications, to maximize peak plasma concentrations and therapeutic efficacy of Belladonna alkaloids and Opium within the immediate postoperative period, and control for variation in procedure length between study participants. The nurses caring for the patient postoperatively will be blinded to which suppository the patient did receive, but will be made aware that the patient had received a suppository containing either glycerin or one containing belladonna 16.2mg and opium 60mg, equivalent to approximately 6mg of morphine. These nurses will be educated about potential side effects of Belladonna & Opium suppositories, and of potential drug interactions; they will be asked to document and to inform the covering provider of the occurrence of any such adverse effects. Patients remaining in the hospital overnight following their surgery will undergo a postoperative exam by a resident physician familiar with the study protocol and familiar with potential side effects of the B&O suppository; this physician will inquire about and document the presence of any such side effects. Standard of care at Mercy Medical Center is for nurses to assess patient’s postoperative pain by visual analog scale at regular time intervals. Data regarding patients’ visual analog pain scores for the first 12 hours following surgery will be extracted from the electronic medical record and analyzed by the research team. PO and IV narcotic use in IV morphine equivalents, PO and IV NSAIDs, and PO and IV antiemetic use will also be assessed over the first 12 following surgery, this data is to be extracted from the electronic medical record and analyzed by the research team. Study surveillance will not extend beyond the duration of the participant's postoperative hospitalization, usually less than 24 hours.

The costs of the Belladonna & Opium Suppettes and glycerin rectal suppositories used in this study will be covered by University of Maryland Medical Center, Department of Obstetrics, Gynecology and Reproductive Sciences as a supported resident research project. The costs of glycerin suppositories will be covered by Mercy Medical Center Pharmacy.

We do not anticipate that study participation will result in any uncovered medical costs, as serious side effects from Belladonna and Opium suppositories are estimated at less than 1% occurrence; however, if such adverse medical reactions were to occur, it would be within the postoperative setting and any associated medical costs would be billed to the patient's insurance company as part of the bundled cost of postoperative care.

Due to their historical use, B&O rectal suppositories have not undergone the rigorous Phase I and II clinical trials required of modern pharmaceuticals seeking FDA approval [1], but are available while the FDA makes determinations of efficacy – a regulatory category shared by drugs hydrocodone and morphine [2,3,4]. Common side effects of B&O suppository are related to anticholinergic activity and include dry nose, mouth, throat, skin, and constipation. Serious side effects are estimated at less than 1% occurrence and include orthostatic hypotension, ventricular fibrillation, tachycardia, palpitation, confusion, drowsiness, headache, loss of memory, fatigue, ataxia, CNS depression, rash, antidiuretic hormone release, bloated feeling, nausea, vomiting, biliary tract spasm, dysuria, urinary retention, urinary tract spasm, increased intraocular pain, blurred vision, weakness, respiratory depression, histamine release, physical and psychological dependence, and diaphoresis [5]. Patients enrolled in this trial would be monitored for development of side effects with review to be performed by investigators on a rolling basis.

Scopolamine is an alkaloid with antiemetic properties that is contained within extract of Belladonna. A scopolamine transdermal patch contains 0.6mg of scopolamine alkaloid, and is sometimes used in the pre-operative setting to reduce nausea and emesis in patients reporting a history of motion sickness or of postoperative nausea and vomiting. The recommended dose of scopolamine for use pre-operatively is 0.3 to 0.65mg [6]. Based on the USP Pharmacopeia and gas chromatography data on belladonna extract [7,8], the B&O rectal suppository contains less than 0.02mg of scopolamine, making the total dose of scopolamine received by a patient with a scopolamine patch and a B&O suppository 0.62mg, which is less than the recommended upper limit of dosing for the operative setting. For this reason, patients receiving a pre-operative scopolamine patch will not be excluded from participation in this trial.

The primary hypothesis of the study is that the use of a B&O rectal suppository is associated with decreased postoperative pain and nausea following total laparoscopic or robot-assisted hysterectomy. The visual analog scale (VAS) to be used for assessment of postoperative pain has been demonstrated to be linear in the setting of mild-to-moderate pain [9], such that a 15% decrease in VAS score corresponds to a 15% decrease in subjectively experienced pain. Minimal clinically significant difference in score on the VAS has been shown to occur at approximately 11-14 mm regardless of pain severity [10]. Sample size calculation is based on VAS pain scores following laparoscopic hysterectomy as reported by Ghezzi, et al. [11]. Sample size is set at 65 patients per group (total trial enrollment of 130 patients) with a goal of detecting a 30% decrease in mean VAS score with 80% power, using $p = 0.05$ as a criteria for statistical significance, and accounting for a rate of up to 15% for trial withdrawal, incomplete data, and loss-to-follow-up [12].

For statistical methodology, patient characteristics for the two study arms will be analyzed using a two-sided Student's t-test for continuous variables, or a χ^2 test for categorical variables and proportions. To assess for clinical superiority of the B&O suppository intervention, one-sided Student's t-test (for continuous outcomes) or a one-sided Fisher's Exact test (for categorical outcomes) will be used. One-sided tests are to be used since the addition of B&O is not expected to increase pain, narcotic use, recovery time, or need for rescue anti-emetics a priori. Fisher's Exact test was chosen as a more conservative measure for assessing outcomes, and due to the availability of a one-sided test. A linear regression will be performed on the outcome of PACU discharge readiness time using several different model specifications in order to check for robustness of results.

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Belladonna and Opium Suppository Study Script

“Because you are scheduled to undergo minimally invasive hysterectomy, you may be eligible to participate in a clinical trial that is underway at our institution. The purpose of this trial is to improve our management of post-operative pain and nausea following minimally invasive hysterectomy. The study looks at whether placement of a medicated rectal suppository at the end of surgery (before waking up from anesthesia) results in less post-operative pain and nausea. A study coordinator for this clinical trial will contact you by phone to discuss your possible involvement in the study.”

Mercy Medical Center - Research Consent Form

Protocol Title: Belladonna and Opium rectal suppository effect on postoperative pain and nausea following Total Laparoscopic and Robot-Assisted Hysterectomy.

Principal Investigator: Dr. Kevin Audlin

- This is a research study. Participation in this study is entirely voluntary – you may choose to opt out of participation in this study at any point. You may interrupt the consent process to ask questions at any time.

PURPOSE OF STUDY

- This is a clinical trial to assess whether a Belladonna and Opium rectal suppository placed at the conclusion of laparoscopic or robot-assisted hysterectomy can reduce pain and nausea following surgery.
- Belladonna & Opium rectal suppositories are a medication that has been in use for over 75 years. Due to their historic use, the Belladonna & Opium rectal suppository is not an FDA-approved medication, but the FDA allows their use (as is the case for morphine and hydrocodone). Recently, the use of the Belladonna & Opium suppository in the postoperative setting has been studied in men undergoing prostate surgery.
- An unmedicated glycerin suppository will be used as a placebo.
- You are being asked to participate in this study because you are undergoing laparoscopic/robot-assisted hysterectomy at Mercy Medical Center
- There will be 130 women participating in this study.

PROCEDURES

- Participants in the study will have a single rectal suppository placed at the end of surgery, **prior to waking up from anesthesia.**
- Half of the study participants will receive a Belladonna & Opium rectal suppository. Half of the study participants will receive an unmedicated glycerin suppository.
- The treatment you get will be chosen by chance, like flipping a coin. You will have an equal chance of being given each treatment. Neither you nor the study doctor will choose what treatment you get.
- The data used in this study is information collected by nurses as part of routine postoperative healthcare. Your participation in the study requires no additional surveys, questions, clinic visits, or telephone calls. Study participation will not extend beyond the duration of your postoperative hospital stay.
- There will be no blood draws or other collection of specimens for this study.

WHAT ARE MY RESPONSIBILITIES IF I TAKE PART IN THIS RESEARCH?

If you take part in this research, you will be responsible for honestly reporting your pain and nausea symptoms to your nurse following surgery up until the time of discharge home from the hospital.

POTENTIAL RISKS/DISCOMFORTS:

- Placement of a rectal suppository may cause mild local discomfort for some patients.
- Common, mild side effects of Belladonna & Opium that you may experience include:
 - Dry nose, mouth, throat, skin, and constipation.
- Rare (less than 1% occurrence), serious side effects of Belladonna & Opium that you may experience include:
 - Low blood pressure with changes in position from sitting to standing, heart arrhythmia or palpitations, fast heart rate, confusion, drowsiness, headache, loss of memory, fatigue, ataxia, CNS depression, rash, decreased urination/urinary retention, pain with urination, bloated feeling, nausea, vomiting, biliary tract spasm, urinary tract spasm, increased eye pain, blurred vision, weakness, difficulty breathing, histamine release, physical and psychological dependence, and sweating.
- Loss of confidentiality of your personal health information is a risk of study participation; to prevent this from occurring, electronic data collected for this study will be secured by password protection, and paper data will be stored in a secure location. If a breach in confidentiality were to occur, you would be notified of what information had been revealed and to whom it was revealed.

POTENTIAL BENEFITS

- You may or may not benefit by taking part in this study. There is no guarantee that you will receive direct benefit from your participation in this study.
- You may experience less postoperative pain and less postoperative nausea as a result of study participation. You may require less narcotic and NSAID medications for control of your postoperative pain, lessening your risk of side effects from these medications.

ALTERNATIVES TO PARTICIPATION

- Your alternative is to not take part in the study. If you choose to not take part, your healthcare at Mercy Medical Center will not be affected. If you do not participate, you will receive routine postoperative pain management including use of narcotics and NSAIDs (non-steroidal anti-inflammatory drugs), and routine postoperative nausea management including use of appropriate antiemetic medications.

COSTS TO PARTICIPANTS

- It will not cost you anything to take part in this study. Neither you, nor your insurance company will be responsible for the cost of medications used in this research protocol.
- We do not anticipate that study participation will result in any uncovered medical costs, as serious side effects from Belladonna and Opium suppositories are estimated at less than 1% occurrence; however, if such adverse medical reactions were to occur, it would be within the postoperative setting and any associated medical costs would be billed to your insurance company as part of the bundled cost of postoperative care.

PAYMENT TO PARTICIPANTS

- Participants will not be paid for their involvement in this study.
- Appropriate medical treatment will be provided if adverse side effects are encountered from the use of the medications under investigation.

CONFIDENTIALITY AND ACCESS TO RECORDS

- All information to be collected for this study will be extracted from the medical record, and then de-identified (a code will be used in lieu of your name or medical record number).
- Efforts will be made to limit access to your personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete secrecy. Organizations that may inspect and copy your information include the IRB other representatives of this organization, the Food and Drug Administration, and the Department of Health and Human Services
- The monitors, auditors, the IRB, the Food and Drug Administration will be granted direct access to your medical records for verification of the research procedures and data. By signing this document you are authorizing this access.
- The data from the study may be published. However, you will not be identified by name. People designated from the Mercy Medical Center and University of Maryland, Baltimore will be allowed to inspect sections of your medical and research records related to the study. Everyone using study information will work to keep your personal information confidential. Your personal information will not be given out unless required by law.
- A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

RIGHT TO WITHDRAW

- **Your participation in this study is voluntary. You do not have to take part in this research. You do not have to agree to participate in this research. If you agree to participate, you are free to withdraw your consent at any time. Refusal to take part or to stop taking part in the study will involve no penalty or loss of benefits to which you are entitled. If you decide to stop taking part, or if you have questions, concerns, or complaints, or if you need to report a medical injury related to the research, please contact the investigator at XXX-XXX-XXXXX, and please contact the Mercy Investigational Review Board at 410-332-9692.**
- If you decide to withdraw from this study, already collected data may not be removed from the study database.

CAN I BE REMOVED FROM THE RESEARCH?

The person in charge of the research study can remove you from the research study without your approval. Possible reasons for removal include change in eligibility for trial (including intraoperative

conversion to open surgery). If you were to be removed from the research study, you would be informed of this change and you would have a chance to ask questions

Signing this consent form indicates that you have read this consent form (or have had it read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form.

If you agree to participate in this study, please sign your name below.

Alternatively, you may choose to opt out of this study – in which case do not sign your name below.

Participant's Signature

Investigator or Designee Obtaining Consent
Signature

Date: _____

Date: _____

Study Participation Alert Form

This patient is participating in study protocol MMC 2015-63 Belladonna and Opium Rectal Suppository Effect on Postoperative Pain and Nausea Following Total Laparoscopic and Robot-Assisted Hysterectomy.

The Principal Investigator is Dr. Kevin Audlin, his contact number is XXX-XXX-XXXX. The resident study coordinator is Dr. Anna Reinert, her contact number is XXX-XXX-XXXX. The Mercy IRB office contact number is 410-332-9692.

This is a randomized, placebo-controlled, double-blinded clinical trial.

This patient has received 1 of 2 drugs, placed rectally at the conclusion of surgery. Either:

1. Belladonna & Opium rectal suppository containing 16.2mg of Belladonna plant extract and 60mg of Opium, equivalent to approximately 6mg of morphine.

or

2. Glycerin suppository (medically inactive placebo)

Neither you, nor the patient will be informed which of the two drugs the patient received. Please treat your patient with routine post-operative care, recognizing that they may have already received the equivalent of 6mg of morphine immediately prior to departure from the OR.

Common side effects of B&O suppository are related to anticholinergic activity and include dry nose, mouth, throat, skin, and constipation. Serious side effect are estimated at less than 1% occurrence and include orthostatic hypotension, ventricular fibrillation, tachycardia, palpitation, confusion, drowsiness, headache, loss of memory, fatigue, ataxia, CNS depression, rash, antidiuretic hormone release, bloated feeling, nausea, vomiting, biliary tract spasm, dysuria, urinary retention, urinary tract spasm, increased intraocular pain, blurred vision, weakness, respiratory depression, histamine release, physical and psychological dependence, and diaphoresis. Please notify the GYN resident/fellow if you suspect that your patient is experiencing any of these serious side effects.