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RESEARCH PROTOCOL

A randomized trial comparing intrathecal morphine and intraoperative lidocaine infusion to epidural anesthesia with postoperative PCA for patients undergoing exploratory laparotomy on the gynecologic oncology service.

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1. SYNOPSIS

Study Title	A randomized trial comparing intrathecal morphine and intraoperative lidocaine IV infusion to epidural anesthesia with postoperative PCA for patients undergoing exploratory laparotomy on the gynecologic oncology service.
Objective	To determine if opioid consumption postoperatively among patients undergoing non-emergent laparotomy by the gynecologic oncology service who receive intrathecal morphine with intraoperative lidocaine (IML) IV infusion are lower than patients who have epidural anesthesia with PCA (EPCA).
Hypothesis	IML will result in a decreased rate of opioid consumption in the postoperative hospital course.
Study Period	Planned enrollment duration: Approximately 8 months Planned study duration: Approximately 12 months
Number of Subjects	174 patients undergoing exploratory laparotomy
Study Design	Prospective, randomized, controlled study.
Inclusion and Exclusion Criteria	**Inclusion Criteria** 1. Female patients ≥18 years old 2. Undergoing non-emergent exploratory laparotomy with the Gynecologic Oncology service 3. No evidence of end organ failure (as stated in 2.3.2 inclusion criteria) **Exclusion Criteria** 1. Patients not giving consent to participate in the study 2. Unable to complete self-report pain questionnaire 3. Moderate to severe kidney or liver failure per lab criteria as outlined 4. Inability to hold anticoagulant medications for a safe amount of time per current ASRA guidelines 5. Contraindication to lumbar puncture or epidural placement, such as known coagulopathy or history of clotting disorders, history of scoliosis or lumbar fusion, infection at site of entry, or current systemic infection 6. Complete bowel obstruction 7. Contraindication to intravenous (IV) lidocaine 8. Current pregnancy or lactation 9. Currently septic 10. Patient currently taking more than 30 MME a day preoperatively 11. BMI >50kg/m^2 12. Intolerance/ contraindication or allergy to receiving non-steroidal anti-inflammatory drugs or acetaminophen or any other medications in the Pre-operative order set
Measurements	1. Morphine Milligram Equivalent (MME) in the postoperative hospital course 2. The rate of postoperative ileus 3. Hospital length of stay 4. Postoperative hypotension. 5. Patient satisfaction with pain control.

	6. Pain scores pre-op, each post-op day inpatient, 2 weeks follow-up and 6 week follow-up. 7. Intravenous bolus volume intraoperatively (mL) and postoperatively (mL) 8. The 30 day readmission rate (#) 9. Operative time (minutes) 10. Rates of DVT and PTE (#) 11. Rate of persistent pain at 6-week follow-up as determined by an NRS pain score greater than or equal to 5

2. STUDY PROTOCOL

2.1 Background and Significance

Enhanced recovery after surgery (ERAS) was established in Europe to decrease variance in how patients were treated postoperatively. This movement has subsequently optimized the patients are cared for in the postoperative setting. Gynecologic oncology guidelines were established in 2016 and include a variety of recommendations within the umbrella of ERAS (Nelson et al, 2016). Four main tenants of ERAS include multi-modal pain control, euvolemia, early ambulation, and early feeding. Two acceptable options for regional anesthesia that fit into the multi-modal approach to pain control within ERAS include epidural anesthesia and intrathecal injections.

Current standard of care at Washington University, Barnes Jewish Hospital (WU/BJH) consists of preoperative bupivacaine epidural placement with patients receiving a PCA (patient-controlled anesthesia) for pain control postoperatively. A recent paper from this institution compared epidural anesthesia to no regional anesthesia for patients undergoing laparotomy while implementing ERAS guidelines. The authors found a decrease in opioid use on day 0 in the epidural group, but equivalent usage on days 1-3 (Huepenbecker et al, 2019). In this study, hospital stay MME approached 200mg in the epidural group, which is significantly higher than other published work (Kjølhede et al, 2019, Colibaseanu et al, 2019). Other studies have found equivalent pain scores and increase opioid use in patients using epidural analgesia when compared with patients with no epidural analgesia (Chen L-M et al, 2009, Belavy et al, 2013).

Historic institutional data has shown the ileus rate to be 11.5% vs 14% (p=0.39) (Huepenbecker et al, 2019), but more recently, in our institution, the ileus rate on the gynecologic oncology service is substantially higher with epidural use. Retrospective data from other institutions have shown lower rates of ileus when using intrathecal injections as a part of ERAS in comparison to the pre-ERAS era which largely used epidurals (2.8% vs 15.7%, $p<0.01$) (Boitano et al, 2018). Similarly, two studies showed slower return of bowel function with epidural usage (Levy et al, 2011; Ackroyd et al., 2020).

Other studies, including two randomized clinical trials have shown an increase length of stay when comparing epidural anesthesia to other forms of postoperative analgesia in both the gynecologic and colorectal surgery literature (Boitano et al, 2018; Kjølhede et al, 2019, Levy et al, 2011; Ackroyd et al., 2020, Belavy et al, 2013). This is particularly important in the age of COVID-19 when length of stay decreases the exposure to patients, most of whom have a cancer diagnosis. Additionally, there is documented increase in intraoperative hypotension and increased fluid bolus with epidural usage (Huepenbecker et al, 2019).

Recently, there has been a national emphasis on decreasing opioid consumption given the addictive and deadly potential for these medications. Opioid related deaths have increased by a factor of six over the

last twenty years (Centers for Disease Control, Atlanta, GA 2020). Studies have shown that one third of chronic opioid users and over 50% of heroin users report being introduced to opioids from the medical profession. In addition, in opioid naïve patients undergoing surgery, approximately 6% become opioid dependent whether they are having major or minor surgery (Callinan et al 2017, Compton et al 2016, Lev et al 2015). This lead the Society of Gynecologic Oncology to release a practice statement in February of 2020 in order to address acute postoperative pain without placing patients at risk for opioid misuse (Kim et al., 2020). The authors advocate for multimodal therapy, however they do not make specific recommendations because "few [strategies] have been evaluated in rigorous trials with gynecologic oncology patients." The purpose of our study is to compare postoperative MME consumption among patients undergoing laparotomy by the gynecologic oncology service who receive epidural anesthesia with PCA (current standard of care) versus intrathecal morphine with intraoperative lidocaine IV infusion. Our hypothesis is patients who receive preoperative intrathecal morphine with intraoperative lidocaine IV infusion will have a lower MME consumption than those who receive epidural anesthesia. Additionally, we believe intrathecal morphine will control patient's pain, allow early feeding, early ambulation, and allow better euvolemia when compared to epidural anesthesia.

2.2 Preliminary Data

Unidentified preliminary data was collected. Briefly, the number of exploratory laparotomy surgeries and MME usage was collected from January through March of 2021. The mean MME consumption in those who received an epidural was 121.30mg. This was done for sample size and rate calculations.

2.3 Objectives:
The primary objective of this study is:

To compare the MME consumption in the postoperative hospital course among patients undergoing laparotomy by the gynecologic oncology service who receive IML versus EPCA.
The secondary objectives of this study are to compare the two treatment groups with respect to:

- Postoperative ileus rate
- Hospital length of stay
- Postoperative hypotension
- Patient satisfaction with pain control
- Pain scores pre-op, post-op day 1, 2 weeks follow-up and 6 week follow-up
- 30 day readmission rate
- Rates of DVT and PTE (collected from day of surgery to 6 weeks after surgery)
- Rate of persistent pain at 6 week follow-up

2.3.1 Subject Selection
Patients undergoing an exploratory laparotomy meeting inclusion criteria will be recruited from the Gynecologic Oncology surgical service.

2.3.2: Inclusion Criteria
1. Female patients ≥18 years old
2. Undergoing non-emergent exploratory laparotomy with the Gynecologic Oncology service
3. No clinical or laboratory evidence of end organ failure:
If available:

- Platelets > 100 K/cumm
- Hemoglobin > 8.0 g/dl
- Serum creatinine <1.5 mg/dl
- Creatine clearance (CrCl) ≥30 based on the original Cockcroft-Gault formula adjusted for weight.
- INR <1.3 reference range
- All other lab values obtained as part of general preoperative work-up must be ≤1.5x normal laboratory value.

2.3.3 Exclusion Criteria

1. Patients not giving consent to participate in the study
2. Unable to complete self-report pain questionnaire
3. Moderate to severe kidney or liver failure per lab criteria as outlined
4. Inability to hold anticoagulant medications for a safe amount of time per current ASRA guidelines
5. Contraindication to lumbar puncture or epidural placement, per acute pain management service such as known coagulopathy or history of clotting disorders, history of scoliosis or lumbar fusion, infection at site of entry, or current systemic infection
6. Complete bowel obstruction
7. Contraindication to intravenous (IV) lidocaine
8. No known pregnancy and not lactating.
9. Currently septic
10. Patient currently taking more than 30 MME a day preoperatively (for >30 days)
11. BMI >50kg/m^2
12. Intolerance/ contraindication or allergy to receiving non-steroidal anti-inflammatory drugs or acetaminophen or any other medications in the Preoperative order set

2.4 Design and Procedures

2.4.1 Study Design:

This is a randomized trial in patients undergoing laparotomy with the Gynecologic Oncology service. Eligible patients will be randomly assigned (1:1) to EPCA (current standard of care at WU/BJH) or intrathecal morphine one time injection (150mcg) with intraoperative lidocaine IV infusion (IML) as previously described (Boitano et al, 2018). Randomization will be stratified by BMI (<30 vs. >/= 30) and surgical complexity scoring (low = score < 3 vs. high = score >/= 3). ERAS protocol with be enforced for both arms.

Number of patients and study sites:

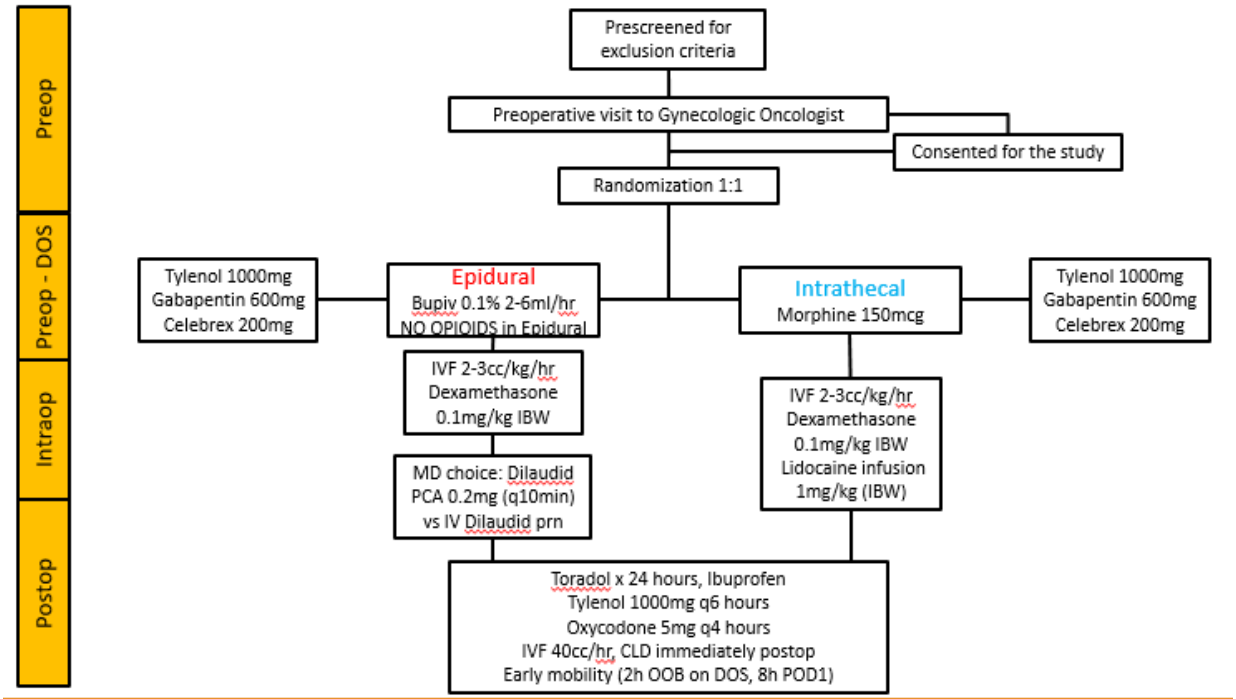
Approximately 174 patients will be recruited at WU/BJH. Allocation is 1:1 resulting in 87 patients allocated to each arm. This is based on detecting a 35mg MME difference with 80% power and alpha of 0.05.

Hypothesis: IML will result in a decreased rate of opioid consumption in comparison to EPCA in the postoperative hospital course

Randomization and Blinding: The study is designed as a randomized clinical trial. It will NOT be blinded as both participants and study staff will know which treatment group each participant is in. Randomization stratification is noted above.

Schema:

*Intrathecal: Intrathecal morphine injection



2.4.2 Pre-Study Period:

Participants will be identified from the Washington University Gynecologic Oncologic service at their preoperative visit for a non-emergent exploratory laparotomy. As is standard for all patients undergoing an exploratory laparotomy, the following screening information will be collected: age, height and weight, known allergies, complete medical history, name and dosing regimen of any over the counter and prescription medications or dietary supplements. We will prescreen all potential participants prior to their pre-operative visit.

Potential subjects meeting all inclusion and exclusion criteria will be consented prior to the surgery. The following will take place at the screening/consent visit:

- Verbal discussion of the study procedures, benefits, and potential risks;
- Subjects reads, understands, and signs informed consent (subjects will also be provided with a fully executed copy);
- Brief history and physical, including vital signs, height and weight measurements, pain history and intensity, surgical complexity score, and medications. A data form for pain history and pain

medications is added as appendix 1.6. The remainder of the information is standard documentation in the history and physical of a preoperative patient.

2.4.3 Study Period

Patients will be enrolled in the study prior to surgery. They will be randomized preoperatively to either EPCA or IML and will be followed daily while inpatient at WU/BJH. They may have scheduled visits at 2 weeks (+/- 1 week) and 6 weeks (+/- 1 week) after surgery as per normal postoperative Gynecologic Oncology protocols. We will call participants who are unable to make their follow-up visits or whose pain information was not collected at the time of their visit.

Surrogates for opioid consumption between discharge and patient postoperative visits will be collected through recording refill of opioid pain prescriptions and emergency room visits. Postoperative pain scores and satisfaction survey will be completed at the postoperative visits and will be completed by phone if a patient is unable to attend the appointment for any reason or does not present.

2.4.4: Minimization of Bias

There will be no specific ethnic, racial, or gender background for enrollment.

2.4.5 Observations and Measurements

IML (Experimental Arm):

Day of Surgery:
Preoperative
- Tylenol 1000mg
- Gabapentin 600mg
- Celebrex 200mg
- Preservative-free intrathecal morphine 150mcg injection (0.15ml or a 0.5mg/0.5ml prepared solution)
- Pulse oximetry will be used on postoperative day 0 on these patients.

Intraoperative
Meds
- Lidocaine IV infusion 1 mg/kg ideal body weight (IBW)

The dose of lidocaine will be 1mg/kg ideal body weight (IBW), calculated by B. J. Devine Formula:

IBW = 45.5 + 2.3 kg per inch over 5 feet (woman)

- Dexamethasone 0.1 mg/kg IBW (up to max of 8mg; 4mg max if diabetic) if no contraindication

Postoperative (DOS)
Meds:
≥80kg and <65years
- Toradol 30mg IV q6 hours x 24 hours
- Ibuprofen 800mg q6 hours (6 hours after last Toradol dose)
- Tylenol 1000mg q6 hours

<80kg or ≥65 years
- Toradol 15mg IV q6 hours x 1 day
- Ibuprofen 600mg q6 hours (6 hours after last Toradol dose)
- Tylenol 1000mg q6 hours

POD1:
≥65 years
- Ibuprofen 600 q6h
- Oxycodone 2.5mg /5mg q4h
- Hydromorphone 0.2mg q2 hours

<65 years
- Ibuprofen 800mg q6h
- Oxycodone 5mg / 10mg q4h
- Hydromorphone 0.4mg q2 hours

EPCA (standard of care arm) protocol:

Day of Surgery
Preoperative
- Tylenol 1000mg
- Gabapentin 600mg
- Celebrex 200mg
- Epidural dosing per standard protocol. Opioids will be restricted from use in the epidural.

Intraoperative
Meds
- Dexamethasone 0.1 mg/kg IBW (up to max of 8mg; 4mg max if diabetic) if no contraindication
- Epidural bupivacaine 0.1% 2-6ml/hr based on MAP within 10% of patient's baseline MAP

Postoperative (DOS)
- Physician's choice of Hydromorphone PCA (standard dosing 0.2mg every 10 minutes, 1.2 mg lockout) versus as needed (prn) intravenous hydromorphone in the amount of hydromorphone 0.2mg q2 hours if ≥65 years and 0.4 q2 hours if <65 years

≥80kg and <65years
- Toradol 30mg IV q6 hours x 24 hours
- Ibuprofen 800mg q6 hours (6 hours after last Toradol dose)
- Tylenol 1000mg q6 hours
- Epidural bupivacaine 0.1% 2-12ml/hr titrated per acute pain service

<80kg or ≥65 years
- Toradol 15mg IV q6 hours x 1 day
- Ibuprofen 600mg q6 hours (6 hours after last Toradol dose)
- Tylenol 1000mg q6 hours
- Epidural bupivacaine 0.1% 2-12ml/hr titrated per acute pain service

POD1:
-If the physicians choice was Hydromorphone PCA then this will be taken down if requirement allows and tolerating PO

≥65 years
- Ibuprofen 600 q6h
- Oxycodone 2.5mg /5mg q4h
- Hydromorphone 0.2mg q2 hours

<65 years
- Ibuprofen 800mg q6h
- Oxycodone 5mg / 10mg q4h
- Hydromorphone 0.4mg q2 hours

ERAS to be followed for both arms:
Prior to day of surgery
- Counseling in clinic RE: ERAS
- Carbohydrate rich drink (ie-Gatorade)

Intraoperative period
- Fluid intraop is 2-3cc/kg/hr for open laparotomy; avoidance of over hydration
- Avoidance of oral, nasogastric, or intra-abdominal drains
- Normothermia
- Appropriate timing of antibiotics

Postoperative period
- IVF 40cc/hr and d/c'd once taking fluids
- CLD immediately postop, advance as tolerated to regular diet within 24 hours
- Encourage use of chewing gum
- Oliguria is permitted, 500cc LR bolus if indicated (x 2 max then move to albumin).
- SCDs plus VTE PPx
- Early mobility (2h OOB on DOS, 8h POD1)

CLD: Clear liquid diet
OOB: Out of bed
IVF: IV fluids

Discharge medications:
This will be completed by a Restrictive Opioid Prescribing Protocol (ROPA)
- Standard discharge medications will be oxycodone 5mg X 15
- Patients with excessive postoperative pain
    - Defined as needing breakthrough medications in the last 24 hours prior discharge
    - Will receive 3x the 24 hour total they received in 5mg or 10mg oxycodone tablets
- Opioid users eligible for the study will be prescribed their normal regimen and similarly be prescribed 3x their breakthrough dosage on discharge (Appendix 1.1).

Refill of opioid pain prescriptions and emergency room visits for pain will be collected.

Postoperative pain scores and satisfaction survey will be completed at the postoperative visits or by phone if a patient is unable to attend the appointment for any reason.

2.4.5.1 Primary Outcome Measures

Primary outcome: Amount of opioid usage in oral morphine milligram equivalents (MME) (conversions present in Appendix 1.2). This will be collected postoperatively while the patient is admitted to the hospital by chart review of the pain medicine tab.

2.4.5.2 Secondary Outcome Measures:

1. The rate of postoperative ileus (defined in Appendix 1.3)
2. Hospital length of stay.
    - Length of stay will be determined by the dates of admission as recorded on EPIC (days).
3. Postoperative hypotension (defined in Appendix 1.4).
4. Patient satisfaction with pain control.
    - Patients will be asked on day of discharge if they were satisfied with their pain control during their hospitalization. They will be able to choose from the following: 1=satisfied, 2= somewhat satisfied, 3= neutral, 4=somewhat dissatisfied, 5=dissatisfied).
5. Pain scores pre-op, each post-op day inpatient, 2 weeks (+/- 1 week) follow-up and 6 week (+/- 1 week) follow-up.
    - Pain scores will be determined by the 0-10 numeric rating scale (NRS)
6. The 30 day readmission rate (#)
7. Rates of DVT and PTE (#)
8. Rate of persistent pain at 6-week (+/- 1 week) follow-up as determined by an NRS pain score greater than or equal to 5

2.4.5.3 Trial Arm Definitions:

IML: Preoperative injection of intrathecal morphine (150mcg) with Lidocaine IV infusion 1 mg/kg ideal body weight (IBW).

EPCA: Epidural bupivacaine 0.1% 2-12ml/hr titrated per acute pain service with hydromorphone patient-controlled anesthesia (PCA). The standard PCA dose is 0.2mg per 10 minutes with a 1.2mg lockout. No bolus of hydromorphone will be ordered.

Statistical Methods:

All demographic, sensory, analytical and patient-reported data will be captured on case report forms, manually entered to a Research Electronic Data Capture (REDCap) database that has been created for the project. The amount of opioid usage in MME will serve as the primary outcome measure for the study. We do not expect missing outcomes data as all primary and most secondary outcomes will be collected with the participants physically present with the research team. Any missing data will be described, but no data imputation will be attempted. Intergroup comparisons for parametric data will be performed by paired t-test, and for non-parametric data by Wilcoxon signed-rank test for paired samples. McNemar's test will be used to compare paired nominal data, and Fisher's exact test to compare non-paired nominal data.

Sample size calculation was based on primary outcome data. Preliminary data shows a mean and standard deviation of postoperative MME with EPCA is 121.3±74.7. Assuming a 5% dropout rate, sample size of 76 per group (152 total) achieve at least 80% power to detect a clinically meaningful MME difference of 35 between the two groups at a significance level of 5% using a two-sided two-sample equal-variance t-test. Powers were calculated using Power Analysis and Sample Size (PASS 15) software. This sample size calculation was increased to 174 total patients to accommodate unanticipated dropout during the COVID pandemic. Allocation is 1:1 resulting in 87 patients allocated to each arm.

The primary analysis will be planned on an intention-to-treat basis regardless of the actual treatment received. Patients will be excluded from the analysis if they withdraw from the study before initiation of anesthesia, if they were no longer eligible for surgery, or if they do not undergo an exploratory laparotomy.

Data Submission Schedule

Case Report Form	Submission Schedule
Original Consent Form	Prior to surgery
Surgical complexity scoring	Prior to surgery
On-Study Form	Prior to surgery
Questionnaire	Following surgery and postoperative visit
Pain scoring	Preoperative appointment Postoperative (daily, duration of hospital stay) 2 weeks (+/- 1 week) post-op 6 weeks (+/- 1 week) post-op
Acute Toxicity Form	During postoperative course while inpatient (chart review and patient reported adverse events)
Late Toxicity Form	6 weeks

All adverse events that occur beginning on the day of surgery (minus exceptions defined in the reporting section) must be captured in the Toxicity Form.

Study Calendar

	Screening	Preop visit	TB	Preop DOS	Surgery	POD	Day of Discharge (+1 day)	2 (+/- 1 week) week postop	6 (+/- 1 week) week postop
Eligible	x								
Surgical consent		x							
Informed consent			x						
Physical exam		x				x		x	x
Exploratory laparotomy					x				
Intrathecal vs epidural placement				x					
Randomization			x						
Adverse events				x		x	x	x	x
Pain scoring		x		x	x	x	x	x	x
Satisfaction questionnaire							x[a]	x[a]	x[a]
Surgical complexity scoring		x							

Preop: Preoperative
Postop: Postoperative
POD: Postopeartive days while inpatient
TB: Time between preoperative visit and surgery – approximately 2 weeks
[a] A 5 question Satisfaction questionnaire to be asked on the day of discharge (+ 1 day); A 2 question pain survey (Q6 from the validated satisfaction questionnaire) to be asked at 2 (+/- 1 week) and 6 (+/- 1 week) post-op visit.

Management of Intercurrent Events

3.1 Adverse Events

The investigators will closely monitor subjects for evidence of systemic adverse events. All adverse events related to participation will be reported and followed until satisfactory resolution. Subjects will notify the monitoring physician/RN coordinator of any adverse experience during the study period. If any patient should suffer any serious side effect, including but not limited to serious neurologic or cardiovascular dysfunction or a reaction concerning for anaphylactic or anaphylactoid reaction, patient recruitment and randomization will be halted until the etiology of such an adverse reaction can be determined.

3.2 Premature discontinuation of protocol for a single patient:

The study protocol may be discontinued prematurely for any patient(s) in the following scenarios:

- Death
- General or specific changes in the patient's condition render the patient unable to receive further treatment in the judgment of the investigator
- Suspected or confirmed pregnancy
- Serious non-compliance with the study protocol
- Lost to follow-up

- Patient withdraws consent
- Investigator removes the patient from study
- Investigator decides to close the study

If a participant withdraws from the study, the participant will be replaced in order to provide the required number of evaluable subjects. Subjects will be withdrawn if the investigator decides that discontinuation is in the best interest of the subject, or the subject requests withdrawal from the study.

3.3 Potential Risks

Lumbar Puncture (LP) for the injection of morphine is widely used technique for post-operative pain control. LP of opioids with local anesthetic is a major clinical tool used in obstetric anesthesia as a fast and safe method to induce surgical conditions for a cesarean section. Intrathecal administration of morphine is a widely accepted procedure for postoperative pain management that is used at multiple academic centers for post-operative pain control (Boitano et al, 2018). An important complication of LP is post-lumbar puncture headache (PLPH) developing within a week after LP. In a multisite international trial, 9% of 3868 enrolled patients reported PLPH [Duits 2016], with 0.3% patients requiring and epidural blood patch (procedure of introducing autologous blood into epidural space). Other adverse events were non-specific headache (10.2%), back pain (17%), nausea and/or vomiting (2.5%), dizziness 45 (1.3%). Other possible complications may include bleeding as well as temporary or permanent neurological damage, although these are extremely rare. Management of these potential adverse events are described below in section 3.4.

Epidural placement

The placement of a thoracic epidural (TE) for acute postoperative pain is currently our standard of care for major abdominal surgeries in which there are no contraindications. And important complication of TE is an inadvertent lumbar puncture and the development of a post-dural puncture headache, back pain, hypotension. Other rare adverse events, include bleeding as well as temporary or permanent neurological damage. Management of these potential adverse events are described below in section 3.4

3.3.1 Procedures to Minimize Potential Risks

Inclusion and exclusion criteria, monitoring, and the clinical protocol are designed to ensure that risks are absolutely minimal. Both arms of the study are routinely performed at multiple institutions. Currently, epidural placement for post-operative pain is our standard of care for these patients. We will be comparing our standard of care to a standard of care at multiple institutions (Boitano et al, 2018). The major differences between our study and standard of care is the recording of various outcomes.

Participants are informed that participation is voluntary and they may refuse to participate and may withdraw from the study at any time without penalty. A pregnancy test will be performed (as is standard on all operative patients) on women of childbearing potential and subjects excluded if pregnant. Subjects will be told that in the event of a physical injury as the direct result of study procedures, they will be cared for by a member of the investigating team at no cost, within the limits of the Washington University compensation plan.

Subjects will be instructed at the beginning of the visit that they can alert the investigator any time they experience bothersome side effects. Medical personnel will be immediately available throughout the visit. The subject can voluntarily withdraw from the study at any time.

With regard to confidentiality; 1) all subjects will be assigned a study ID number, 2) Samples will be kept confidentially. They will be coded, with a key to the code linking code numbers to names kept at a separate location, under lock and key. 3) The link to identifiers will be destroyed at the end of the study.

4) Data will be stored under lock and key (office, file cabinet) and only the investigators and research team will have access. If data are published, there will be no link to identifiers.

3.3.2 Preparation and Administration of Intrathecal Morphine

The morphine preparation is a preservative free compounded solution regularly prepared by the BJH pharmacy in a 0.5mg/0.5ml in a 3mL syringe. We will use the 0.5mg/0.5ml pharmacy prepared product with the plan to administer 0.15mg (150mcg) per patient. 0.15ml will be drawn up using a sterile insulin syringe with attending physician present and then mixed with 2mL of preservative free normal saline in a 5mL syringe prior to injection. Dilution of the morphine will minimize the amount of medication lost in the dead space of the needle. This strategy is similar to standard practice for intrathecal morphine administration by the obstetric anesthesia service and will be applied to this study.

3.3.3 Prevention, diagnosis and management of post-lumbar puncture headache (PLPH)

Lumbar puncture and intrathecal morphine injection will conducted in a way to minimize the effect of risk factors contributing PLPH development. Particularly, an atraumatic needle of 24 G diameter will be used for LP procedure.

Subjects will be asked to notify clinical personnel immediately if they develop a positional headache while in the hospital. Additionally, the periodic nursing assessment performed routinely but the nurses include questions about pain such as headache. If a participant endorses new-onset positional headache, the anesthesiologist on the Acute Pain Service will be notified. The anesthesiologist will perform a brief history and physical exam to determine whether or not the symptoms suggest PLPH. If PLPH is likely and symptoms are mild, conservative treatment will be initiated. The participant will be encouraged to lie in a comfortable position and drink fluids. The subject will also be offered analgesics including acetaminophen/butalbital/caffeine (e.g. Fioricet®), ibuprofen, or acetaminophen alone. IV fluids or medication will be reserved for subjects who cannot tolerate oral administration due to nausea/vomiting. If symptoms are severe (e.g. uncontrollable nausea/vomiting, severe subject distress), the subject will be removed from the study and epidural blood patch will be offered (procedure described below).

Discharge paperwork will include clear descriptions of PLPH and instructions about whom to contact in the case of headache. If a subject reports likely PLPH by contacting study personnel or during a follow-up phone call, symptom severity will be assessed. Conservative treatment (as described above) will be offered for the first 24-48 hrs. Although rare, any unresolved post-dural puncture headache in either group would be treated per standard of care by the inpatient pain service.

Epidural blood patches are commonly performed by our Acute Pain Service. Using sterile technique (including chlorhexidine swabs, caps, masks, and sterile gloves). First, the provider locates the epidural space using a standard Tuohy needle and loss-of-resistance technique. Second, the provider obtains approximately 20ml of the subject's blood, which is then injected through the Tuohy needle. Injection is stopped if the subject complains of pressure or paresthesia that could indicate compression of the cauda equina.

3.4 Prevention, diagnosis and management of other intrathecal catheter-related complications

The potential complication of epidural hematoma is exceedingly rare in patients with normal coagulation (Duits 2016). To minimize the risk of epidural hematoma, subjects will be asked about a history of clotting disorders, easy bleeding/bruising, liver disease, or use of anticoagulants. If indicated, a

complete blood count will be drawn during the screening visit to rule out thrombocytopenia. Any potential subject with abnormalities on history or lab work will be excluded from the study.

To minimize the risk of infection or nerve damage from lumbar puncture or epidural placement, the procedure will be done by experienced anesthesia personnel (board-certified or board-eligible anesthesiologists) under sterile conditions. Specifically, the subject's lumbar region will be sterilized with a chlorhexidine or duraprep swab, a sterile drape will be placed, the anesthesiologist will wear sterile gloves, all personnel in the room will wear a cap and mask, and a sterile occlusive dressing will be applied after LP or epidural catheter. Subjects will be instructed to notify the anesthesiologist of the occurrence and resolution of any paresthesia during LP or epidural procedure. If symptoms are severe (e.g., severe pain, motor deficits) the subject will be sent to the BJH ED for further evaluation including neurology consultation, imaging, or hospital admission, as needed. Subjects with temporary, minor paresthesia during placement may continue with the study.

Regulatory and Reporting Requirements
The entities providing oversight of safety and compliance with the protocol require reporting as outlined below. Please refer to Appendix 1.7 for definitions and Appendix 1.8 for a grid of reporting timelines.

Adverse events will be tracked from the day of surgery (pre-op) through 6 weeks following day of surgery. All adverse events must be recorded on the toxicity tracking case report form (CRF).

Refer to the data submission schedule for instructions on the collection of AEs in the EDC.

Reporting to the Human Research Protection Office (HRPO) at Washington University

Reporting will be conducted in accordance with Washington University IRB Policies.

Pre-approval of all protocol exceptions must be obtained prior to implementing the change.

Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI (or designee) is required to notify the QASMC of any unanticipated problems involving risks to participants or others occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to qasmc@wustl.edu. Submission to QASMC must include the myIRB form and any supporting documentation sent with the form.

Exceptions to Expedited Reporting

Events that do not require expedited reporting as described above include:

- Planned hospitalizations
- Hospitalizations < 24 hours
- Respite care
- Events related to disease progression

Events that do not require expedited reporting must still be captured in the EDC.

3.5 Data and Safety Monitoring Plan

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, and commensurate with the risks of the proposed study, we will use an Independent Medical Monitor for data safety and monitoring for this study. The potential risks are attributable to intrathecal morphine administration or thoracic epidural placement. The Independent Medical Monitor will be an anesthesiologist who is not involved in the study, and who is knowledgeable in the risks associated with intrathecal morphine administration and thoracic epidural placement. This individual will review the annual summary of adverse events, prior to data and safety monitoring report submission to the Washington University IRB. In addition, this individual will review all reports of a Serious Adverse Event, or an Unexpected Adverse Event.

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities that are unexpected, related, and place the subject at greater risk. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO according to institutional guidelines.

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least one patient has been enrolled) or one year after accrual has opened (if no patients have been enrolled at the six-month mark).

The Principal Investigator will review all patient data at least monthly (or before each treatment escalation if occurring sooner than monthly) and provide a semi-annual report to the QASMC. This report will include:

• HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician.
• Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
• History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason.
• Study-wide target accrual and study-wide actual accrual
• Protocol activation date
• Average rate of accrual observed in year 1, year 2, and subsequent years
• Expected accrual end date and accrual by cohort
• Objectives of protocol with supporting data and list the number of participants who have met each objective
• Measures of efficacy
• Early stopping rules with supporting data and list the number of participants who have met the early stopping rules.
• Summary of toxicities separated by cohorts with the number of dose-limiting toxicities indicated
• Abstract submissions/publications
• Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

4. HUMAN SUBJECTS RESEARCH

4.1 Protection of Human Subjects

The study will be conducted under appropriate Washington University Institutional Review Board protocols and consent forms approvals. The study will be conducted under the supervision of the co-PIs who is a gynecologic oncology surgeon with several years of experience in the conduct of human studies; a board-certified anesthesiologist and board-certified pain management specialist as co-PI, with extensive clinical and human research experience; and a sixth year surgical fellow physician.

4.2 Sources of Materials

Subjects will be recruited from the greater Saint Louis area via their Washington University Gynecologic Oncologic physicians. Data on comorbidities and concomitant medication use are provided by subjects. No specimens will be collected that are not used directly in their perioperative care.

4.3 Recruitment and Informed Consent

Participants will be recruited through their Washington University Gynecologic Oncologic physicians. We may also screen the clinic schedule of the Washington University Gynecologic Oncologic physicians, to identify potentially eligible subjects. We will then approach or contact them to ask for their interest in the study. Subjects will be given verbal (initially) and then written descriptions of the study aims, procedures, risks, and benefits, and will be required to give written informed consent. A member of the study team provides all study descriptions, informed consent, and answers all questions. Subjects are informed verbally and in writing that participation is voluntary and they may refuse to participate and may withdraw from the study at any time without penalty.

4.4 Potential Benefits of the Proposed Research to the Subjects and Others

Study subjects could potentially experience improvement in ileus rates or earlier discharge. Society could benefit from development of clear evidence on the best perioperative regiment for exploratory laparotomy for gynecologic surgery.

4.5 Inclusion of Women

Only women will be included in this study as men do not undergo gynecological surgery.

4.6 Inclusion of Minorities

All of our studies actively encourage the participation of minorities in the research. Our minority recruiting typically matches the demographic composition of the Washington University community from which subjects will be recruited (78% white, 21% Black, <1 % Hispanic).

4.7 Inclusion of Children

Children <18 years of age will not be studied in this investigation. Exploratory laparotomies are uncommon in this age group.

Appendix 1.1: Validated tier system for restrictive opioid prescribing protocol (ROPA)

Tier	Procedure	Medications
1	Minor procedure (i.e. dilation and curettage, exam under anesthesia, cold knife cone, etc.)	No opioids prescribed
2	Laparoscopic procedure (laparoscopic hysterectomy and robotic hysterectomy, etc.)	Oxycodone 5 mg × 5 tabs
3	Major procedure (abdominal hysterectomy, laparotomy, staging procedures, etc.)	Oxycodone 5 mg × 15 tabs
4A	Chronic opioid use	Oxycodone 5–10 mg tabs[a]
4B	Excessive postoperative pain	Oxycodone 5–10 mg tabs[a]
All patients take scheduled acetaminophen and NSAIDs unless contraindicated		

[a] Three times the amount used in the last 24 h.

Appendix 1.2: Oral morphine milligram equivalents (MME) with the following conversions:

The conversion from intrathecal (IT) morphine to IV morphine is 1:100

- Conversion of IV morphine to PO morphine is 1:3
- 150mcg IT morphine is 15 mg IV morphine
- Conversion of IV hydromorphone to PO morphine is 1:20 (1 mg IV hydromorphone is 20 mg PO morphine)
- Conversion from oral opioids such as oxycodone to oral morphine will be done using the conversion factors published by CDC.gov (see below).

Opioid Oral Morphine Milligram Equivalent (MME) Conversion Factors[1,2]

Type of Opioid (strength units)	MME Conversion Factor
Buprenorphine film/tablet[3] (mg)	30
Buprenorphine patch[4] (mcg/hr)	12.6
Buprenorphine film (mcg)	0.03
Butorphanol (mg)	7
Codeine (mg)	0.15
Dihydrocodeine (mg)	0.25
Fentanyl buccal or SL tablets, or lozenge/troche[5] (mcg)	0.13
Fentanyl film or oral spray[6] (mcg)	0.18
Fentanyl nasal spray[7] (mcg)	0.16
Fentanyl patch[8] (mcg)	7.2
Hydrocodone (mg)	1
Hydromorphone (mg)	4
Levorphanol tartrate (mg)	11
Meperidine hydrochloride (mg)	0.1
Methadone[9] (mg)	
>0, <= 20	4
>20, <=40	8
>40, <=60	10
>60	12
Morphine (mg)	1
Opium (mg)	1
Oxycodone (mg)	1.5
Oxymorphone (mg)	3
Pentazocine (mg)	0.37
Tapentadol [10] (mg)	0.4
Tramadol (mg)	0.1

Appendix 1.3: Definition of ileus

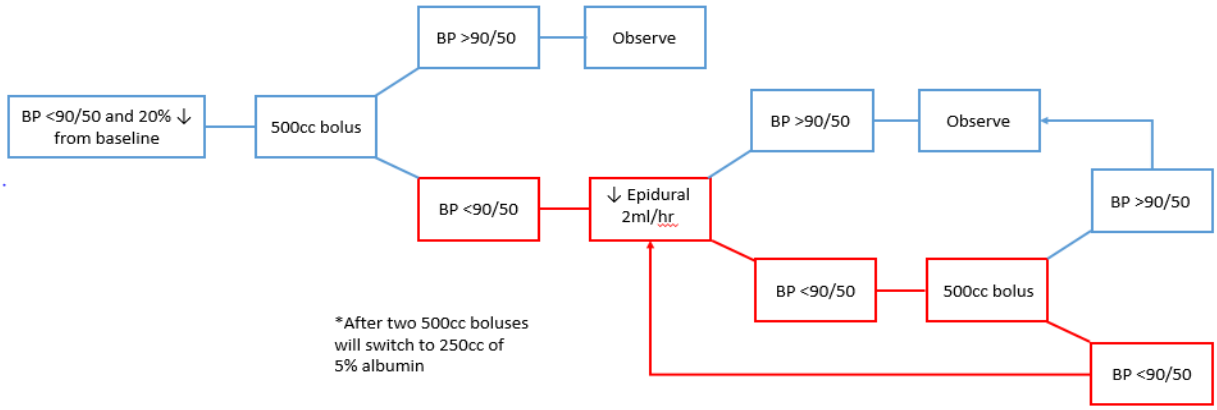
Defined by bilious emesis requiring a change in diet to nothing-per-mouth (NPO) status or nasogastric tube placement (NGT) in the absence of other indications. Patients who had NGT placed prophylactically at the time of surgery were not considered to have an ileus unless an NGT was reinserted or they met the above criteria. Participants will be assigned a value of yes ileus or no ileus. The rate of post op ileus is defined as the observed number of yes ileus in each study arm divided by the total number of subjects in the study arm. Fisher's exact test will be used to compare non-paired nominal data.

Appendix 1.4: Definition of postoperative hypotension

Definition: Postoperative hypotension will be defined as <90/50 (as previously defined by Huepenbecker, et al.) or a 20% decrease from the preoperative office visit.

Management: If a patient has a blood pressure <90/50 and it is determined that their preoperative blood pressure was over 20% higher than either their systolic or diastolic blood pressures, the house staff physician managing the floor will bolus 500cc of lactated ringers or normal saline (0.9%). If the hypotension does not resolve the house staff physician should turn down the epidural by 2 ml/hr and monitor with an option to deliver an additional 500cc of lactated ringers or normal saline (0.9%). The remainder of resuscitation should occur with 250cc of 5% albumin. If patient remains <90/50 the house staff physician should turn down the epidural by an additional 2ml/hr. Once the blood pressure increases to >90/50 the physician should observe. Blood products will also be recorded separately as postoperative resuscitation.

Hypotension algorithm



Appendix 1.5: Surgical Complexity scoring (via Alletti et al., 2007)

Procedure	Points
TH-BSO	1
Omentectomy	1
Pelvic lymphadenectomy	1
Paraaortic lymphadenectomy	1
Pelvic peritoneum stripping	1
Abdominal peritoneum stripping	1
Rectosigmoidectomy_T-T anastomosis	3
Large bowel resection	2
Diaphragm stripping/resection	2
Splenectomy	2
Liver resection/s	2
Small bowel resection/s	1

Complexity score groups	Points
1 (low)	3 or fewer
2 (intermediate)	4-7
3 (high)	8 or more

TH-BSO, total hysterectomy-bilateral salpingo-oophorectomy.

Aletti. Relationship among surgical complexity, short-term morbidity, and overall survival in primary surgery for advanced ovarian cancer. Am J Obstet Gynecol 2007.

Appendix 1.6: Data Form

Questions to be asked a preoperative visit

1. Are you currently in pain? If so, what is the severity of your pain 0-10?
2. Have you ever seen a pain medicine specialist?
3. Have you ever taken narcotic pain medication for over 30 days consecutively?
4. When was the last time you consistently took narcotic pain medicine for over 30 days consecutively?
5. Are you taken narcotic pain medicine currently? If so, what amount?

Questions to be asked a the 2 week and 6 week post-operative visits

1. After you were discharged from the hospital, did the medications help to relieve your pain? Please rate the level of pain control on a scale of 1 (not good) to 5 (very good). If you did not require pain medication at home, select NA.
2. Are you currently in pain? If so, what is the severity of your pain 0-10?

Appendix 1.7: Definitions for Adverse Event Reporting

A. Adverse Events (AEs)

As defined in 21 CFR 312.32:

Definition: any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website: http://www.hhs.gov/ohrp/policy/advevntguid.html

B. Suspected Adverse Reaction (SAR)

As defined in 21 CFR 312.32:

Definition: any adverse event for which there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. "Suspected adverse reaction" implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

C. Life-Threatening Adverse Event / Life Threatening Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: any adverse drug event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator, its occurrence places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

D. Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: an adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Any other important medical event that does not fit the criteria above but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

E. Protocol Exceptions

Definition: A planned change in the conduct of the research for one participant.

F. Deviation

Definition: Any alteration or modification to the IRB-approved research without prospective IRB approval. The term "research" encompasses all IRB-approved materials and documents including the detailed protocol, IRB application, consent form, recruitment materials, questionnaires/data collection forms, and any other information relating to the research study.

A minor or administrative deviation is one that does not have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

A major deviation is one that does have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

Expedited Reporting Timelines		
Event	**HRPO**	**QASMC**
Unanticipated problem involving risk to participants or others	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	Report via email after IRB acknowledgment
Major deviation	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	
A series of minor deviations that are being reported as a continuing noncompliance	Report within 10 working days.	
Protocol exception	Approval must be obtained prior to implementing the change	
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.	
Breach of confidentiality	Within 10 working days.	
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.	

Routine Reporting Timelines		
Event	**HRPO**	**QASMC**
Adverse event or SAE that does not require expedited reporting	If they do not meet the definition of an unanticipated problem involving risks to participants or others, report summary information at the time of continuing review	Adverse events will be reported in the toxicity table in the DSM report which is typically due every 6 months.
Minor deviation	Report summary information at the time of continuing review.	
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.	
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days.	

	If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.	