A Non-Inferiority Randomized Trial Comparing the Impact of Thoracic Epidural Analgesia Versus Surgical Site Infiltration With Liposomal Bupivicaine on the Postoperative Recovery of Patients Following Open Gynecologic Surgery

NCT04117074

11/06/2022

JHM IRB - eForm A – Protocol

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1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Problem: Innovation of Enhanced Recovery After Surgery (ERAS) programs for implementing evidence-based, multidisciplinary perioperative care protocols has occurred in response to recent quality and safety mandates in surgery. Key ERAS components include use of opioid-sparing multimodal perioperative analgesia (including loco-regional anesthesia), perioperative goal-directed fluid therapy and early refeeding and mobilization. A 2012 Cochrane review as well as several large retrospective and prospective studies of ERAS programs in gynecologic oncology and colorectal surgery indicate that implementation of these care pathways is associated with improved pain management, decreased narcotics use, reduced length of stay and cost reductions with stable readmission, postoperative complication and mortality rates.[1-4]

Thoracic epidural analgesia (TEA) has been a key part of opioid-sparing multimodal perioperative analgesia since ERAS was introduced over a decade ago in Europe. Many randomized controlled trials have focused on the benefits of TEA, which have demonstrated that TEAs are effective in attenuating the surgical stress response and reducing pain and opioid consumption for up to 72 hours (h) following abdominal incisions. TEA also has an impact on complications following abdominal surgery, reducing the time to bowel recovery by up to 36 h and may reduce cardiac and respiratory complications in high-risk patients.[6-8] While analgesia and recovery seem to be better with TEA than intravenous opioid patient controlled analgesia (PCA), the value of TEA compared to other loco-regional nerve blocks for patients on ERAS programs following open gynecologic surgery is unknown. TEA failure rates are as high as 30% and many of these patients will require supplemental opiates.[9] TEA is also expensive.

Given these disadvantages, some leading ERAS programs use surgical site infiltration with long acting local anesthetics in lieu of TEA. Extended-release liposomal bupivacaine (LB) was recently approved by the FDA for single-dose surgical site infiltration to produce postsurgical analgesia. Cost and concerns for reimbursement for LB have hindered approval of LB within pharmacy formularies. However the cost of TEA exceeds that of LB. The cost of one 20mL single vial use of LB is less than or equal to the cost of a continuous epidural kit and does not incur the additional costs of TEA: 1) professional fees for placement and daily management and 2) use of operating room time for placement, which is estimated at $14 per minute at our institution. To date, there has never been a comparison between the analgesic efficacy of TEA and LB surgical site infiltration following open abdominal surgery.

Hypothesis: The goal of this project is to test the hypothesis that surgical site infiltration with LB is non-inferior to and more cost effective than TEA for patients undergoing open gynecologic surgery on an established ERAS program using a non-inferiority randomized trial design. The impact of TEA and

surgical site infiltration with LB on neuroendocrine and inflammatory mediators of the surgical stress response (SSR) will also be investigated as a translational endpoint.

Importance of Research: This study would be the first randomized trial comparing the value of the two prevailing modalities of loco-regional analgesia (TEA and LB surgical site infiltration) used by ERAS programs for open abdominal surgery in the U.S. The proposed value analysis is unique in accounting for a wide spectrum of quality, outcome and cost variables. Further, it has potential to set a precedent for quantifying the impact of discrete ERAS components on the surgical stress response. While the concept and theory behind surgical stress are old, little is known about its pathophysiology in the era of modern surgery. Results from this study would also better define the optimal non-opioid pain management regimen for patients recovering from open abdominal surgery and are urgently needed by the American College of Surgeons (ACS) and the Society of Gynecologic Oncology (SGO) in formulating our national ERAS guidelines as well as strategies for opioid reduction.

2. Objectives (include all primary and secondary objectives)

Primary objectives:

To test the hypothesis that surgical site infiltration with liposomal bupivacaine (LB) is non-inferior to thoracic epidural analgesia (TEA) using the coprimary efficacy endpoints: (1) the mean Area under the Curve (AUC) of visual analog scale (VAS) pain intensity scores from 0 to 48 hours postoperatively and (2) total opioid consumption (IV morphine equivalents, mg) from 0 to 48 hours postoperatively.

Coprimary efficacy endpoints will be used to test the hypothesis that surgical site infiltration with LB is non-inferior to TEA: (1) the mean Area under the Curve (AUC) of visual analog scale (VAS) pain intensity scores from 0 to 48 hours postoperatively and (2) total opioid consumption (IV morphine equivalents, mg) from 0 to 48 hours postoperatively will be compared between the two treatment groups. The mean AUC of VAS pain intensity scores endpoint incorporates the use of rescue medications by using an imputation method called windowed worst observation carried forward (WWOCF). This method imputes a subject's pain score as their worst pain score for a pre-specified window after a rescue medicine. Subjects will be evaluated for pain intensity at rest at 6, 12, 18, 24, 30, 36, 42, 48, and 72 hours after surgery and then once daily (at noon ± 4 hours) through postoperative day 14. Subjects will also record an unscheduled pain score immediately before any requested opioid pain medication. The exact time of the assessment will be recorded to limit variability. Total opioid consumption in IV morphine equivalents (mg) during the first 48 hours postoperatively will be tracked for each subject.

Secondary objectives:

To compare the impact of TEA and surgical site infiltration with LB on patient reported and clinical outcomes as well as on neuroendocrine and inflammatory mediators of the surgical stress response using the following measures:

1. Mean patient-perceived quality of recovery score on postoperative days 1-7 (QoR-15).
2. Time to return of bowel function (ROBF) and incidence of postoperative ileus.
3. Mobility Level.
4. Degree of sedation.
5. Length of hospital stay and time (in days) to meeting discharge criteria.
6. Total intravenous fluids administered and time to postoperative diuresis.
7. Need for vasopressors (amount and duration).
8. Incidence of major postoperative complications, including 30-day hospital readmission.

9. Total direct costs associated with loco-regional anesthesia.
10. Post-discharge narcotic utilization.

1. Mean patient-perceived quality of recovery score on postoperative days 1-7. Patient-perceived quality of recovery will be assessed using the Quality of Recovery score (QoR-15) which is a validated instrument designed to measure the major domains of postoperative recovery including functional independence, physical comfort/pain, psychological/emotional well-being, cognition and satisfaction (Appendix A). Quality of recovery will be measured using this instrument on the first postoperative day and each day thereafter (at noon ± 4 hours during a period of rest) during inpatient hospitalization to and including the day of discharge or postoperative day 7 (whichever comes first) in order to obtain longitudinal data about the quality of recovery experienced by patients. Patients unable to complete the questionnaire independently will be asked for verbal responses to each item.
2. Time to return of bowel function (ROBF) and incidence of postoperative ileus. Time to ROBF will be defined as the time lapse from the day of surgery (DOS) to the day oral intake is tolerated for 48 hours without vomiting. Ileus is defined as the occurrence of postoperative nausea and vomiting requiring cessation of oral intake and initiation of intravenous hydration +/- nasogastric tube placement following documented ROBF or the persistence of these symptoms beyond postoperative day 5 in the absence of ROBF.
3. Level of mobilization. Preoperative baseline mobility will be assessed using the Boston University AM-PAC Surgical Short Form per our standard practice. On the first postoperative day and each day thereafter through date of discharge or postoperative day 7 (whichever comes first), mobility will be assessed using the 8-point validated JH-HLM scale. Need for formal physiotherapy consultation will also be recorded.
4. Degree of sedation. Degree of sedation will be assessed on each postoperative day through the date of discharge or postoperative day 7 (whichever comes first) at noon ± 4 hours using the Pasero Opioid Induced Sedation Scale (Appendix B).
5. Length of hospital stay and time (in days) to meeting discharge criteria. Often, patients remain inpatient beyond the time at which they first meet discharge criteria due to a variety of psychosocial factors. Thus, length of hospital stay and time (in days) to meeting discharge criteria will be separately recorded. Discharge eligible criteria include: (1) hemodynamically stable, (2) afebrile, (3) ROBF, (4) pain controlled with oral analgesics, (5) independence with ADLs, (6) walking greater than 250 feet.
6. Total intravenous fluids administered and time to postoperative diuresis defined as the time lapse from date of surgery (DOS) to a net negative fluid balance sustained over a 24 h time period.
7. Need for vasopressors (amount and duration).
8. Incidence of major postoperative complications, including 30-day hospital readmission.
9. Total direct costs associated with loco-regional anesthesia: The analysis will include the direct variable cost of supplies and pharmacy (including initiation of PCA in the event of block failure) as well as anesthesia professional fees (TEA only; both intraop and postop) and cost of OR time in minutes to perform the blocks.
10. Post-discharge narcotic utilization. Total outpatient narcotic use during the immediate outpatient postoperative period will be obtained from the patient by nurse phone survey on postoperative day 14, provided the patient is outpatient and not still admitted or readmitted to the hospital.

Translational Endpoints:

1. Biomarkers of surgical stress response. Blood samples (10mL of whole blood) will be collected on the DOS when routine IV access is established in preop or the operating room and postoperative days 1 through postoperative day 7 coinciding with routine IV access for blood, for analysis of peripheral blood counts. Blood collection on postoperative day 0 is optional. Serum will

be isolated and banked in Dr. Shih's laboratory for ELISA by his research team and the SOM Onc Human Immunology Core in order to measure circulating levels of ACTH, epinephrine, total cortisol, ADH, interleukins, ANP, syndecan-1, glycosominoglycans, endothelial glycocalyx constituents, CRP and TNF-α. Saliva (1mL) will also be collected by patients at 6PM preoperatively and at 6PM±1hr postoperatively thereafter through the first 7 days after surgery for cortisol measurement by ELISA since measurements of salivary cortisol more accurately reflect serum free cortisol concentrations than do measurements of serum total cortisol. Saliva collection on postoperative day 0 is optional and mandatory on postoperative days 1-7. The salivary collection protocol has previously been published.[10]

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Innovation of ERAS programs for implementing evidence-based, multidisciplinary perioperative care protocols has occurred in response to recent quality and safety mandates in surgery. These programs are also important mechanisms for achieving value-based improvements in surgical care. Johns Hopkins Hospital (JHH) is an authoritative leader in the national ERAS initiative. The JHH colorectal and gynecologic oncology ERAS programs are identical and well-established in their respective fifth and third years of existence. These programs were developed within the JHH Colorectal Comprehensive Unit Safety Program (CUSP) by surgeons, anesthesiologists, nurses and pharmacists. The fundamental goal of these and other ERAS programs is to preserve normal physiologic function postoperatively by reducing surgical stress. Key ERAS components include use of opioid-sparing multimodal perioperative analgesia (including loco-regional anesthesia), perioperative goal-directed fluid therapy and early refeeding and mobilization. A 2012 Cochrane review as well as several large retrospective and prospective studies of ERAS programs in gynecologic oncology and colorectal surgery indicate that implementation of these care pathways is associated with improved pain management, reduced length of stay and substantial cost reductions with stable readmission, postoperative complication and mortality rates.[1-4] Further, given that upwards of 10% of patients develop opioid dependence after being exposed to these medications following an operation, non-opioid pain management protocols championed by ERAS programs play an instrumental role in addressing the U.S. opioid epidemic.[5]

Many randomized controlled trials over the past 20 years have focused on the benefits of TEA. TEA is effective in attenuating the surgical stress response and reducing pain and opioid consumption for up to 72 hours (h) following abdominal incisions, and also has an impact on complications following abdominal surgery, reducing the time to bowel recovery by up to 36 h and may reduce cardiac and respiratory complications in high-risk patients.[6-8] While analgesia and recovery seem to be better with TEA than intravenous opioid patient controlled analgesia (PCA), the role of TEA in pain control for patients on ERAS programs following open gynecologic and colorectal surgery is controversial. TEA failure rates are as high as 30% and many of these patients will require supplemental opiates.[9] The sympathetic block that results from TEA commonly results in hypotension that results in at least temporary discontinuation of the infusion, prompts intravenous fluid administration to already volume overloaded patients and may require treatment with vasopressors.[11] TEA may hinder achievement of other ERAS goals such as mobilization and removal of urinary catheters, and TEA has been shown to increase length of hospital stay and complication rates in gynecologic cancer surgery.[12, 13]

Given these disadvantages, some leading ERAS programs use surgical site infiltration with long acting local anesthetics in lieu of TEA. Extended-release liposomal bupivacaine (LB) was recently approved by the FDA for single-dose surgical site infiltration to produce postsurgical analgesia. The liposomal preparation consists of microscopic multi-vesicles with a lipid-soluble lining and an aqueous core containing encapsulated bupivacaine allowing it to be slowly released over a period of up to 72–96 h.[14] Existing data indicate that surgical site infiltration with LB following mammoplasty and open colectomy decreases postoperative opioid requirements and length of stay.[15, 16] Recently, the Mayo Clinic published their

experience with abdominal incision injection of LB versus standard bupivacaine hydrochloride after laparotomy for gynecologic malignancies. Compared to bupivacaine hydrochloride, abdominal incision infiltration with LB was associated with less opioid consumption as well as lower rates of postoperative nausea and ileus. Pain scores, length of hospital stay and total pharmacy costs did not differ between the groups.[17]

To date, there has never been a comparison between the analgesic efficacy of TEA and LB surgical site infiltration following open abdominal surgery. In many cases, cost and concerns about reimbursement have hindered approval of LB within hospital formularies. These concerns stem from Centers for Medicare and Medicaid Services (CMS) mandated bundling of reimbursement for all drugs used during a surgical procedure with the procedure itself as well as from inconsistencies in contracts between hospitals and private/commercial insurers regarding payment policies for separately payable drugs. However, the cost of TEA significantly exceeds that of LB. The cost of a 20 mL single use vial of LB is less than or equal to the cost of a continuous epidural kit. TEA incurs the added expenses of (a) professional fees for placement and daily management and (b) the use of operating room (OR) time for placement (~$14 dollars/min at our institution). Currently on the JHH gynecologic oncology ERAS program, 40% of epidurals are placed in the OR with an average OR time expenditure of 30 minutes per epidural. Additional pharmacy costs also accumulate in the 30% of cases of failed TEA.

Despite the expense, TEA has been the preferred modality of loco-regional analgesia for many ERAS programs at our institution, including the Gyn-Oncology ERAS program, because of the prevailing theory that TEA is superior to other modalities in reducing the surgical stress response. The surgical stress response (SSR) encompasses the hormonal, metabolic, immunologic, and inflammatory changes that follow the physical trauma of surgery in order to arrest ongoing tissue damage, prevent infection, and activate repair processes necessary to restore normal function. The early phase of this process is characterized by a series of changes, including activation of hypothalamic–pituitary–adrenal axis with release of adrenocorticotropic hormone (ACTH) leading to an increase in plasma cortisol and secretion of endogenous catecholamines. The SSR initiates a cascade of inflammatory responses mediated by several substances with cytokines, such as IL-6, playing a key role. They act as pro- and anti-inflammatory effectors by stimulating or dampening the activation of immune cells and release of more cytokines. Amplitude and/or time dependent perturbations in SSR mediators may result in decreased cell mediated immunity, fatigue, fluid imbalance, and cognitive dysfunction throughout the postoperative course.[18] To the best of our knowledge, the impact of loco-regional analgesia with TEA versus LB surgical site infiltration on neuroendocrine and inflammatory mediators of SSR in the context of an ERAS program has never been investigated.

Thus, the goal of this project is to test the hypothesis that surgical site infiltration with LB is non-inferior to and more cost effective than TEA for patients undergoing open gynecologic surgery on an established ERAS program using a non-inferiority randomized trial design. The impact of TEA and surgical site infiltration with LB on neuroendocrine and inflammatory mediators of SSR will also be investigated as a translational endpoint.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

Participation will be offered to patients undergoing a planned laparotomy on the gynecologic oncology service. Patients will be identified from gynecologic oncology pre-operative clinics. Eligible participants will be stratified based on pre-operative likelihood of malignancy (into likely benign disease vs. likely malignant disease). This stratification will be based upon the surgeon's preoperative impression of likelihood of malignancy. Participants will then be randomized 1:1 via a stratified randomized technique by the inpatient pharmacy on the day of enrollment to the following arms:

1. Thoracic epidural analgesia: 0.125 % Bupivicaine (5-7 cc per hour) throughout the entire case with a 3cc bolus at the end of the procedure just prior to emergence. Postop 0.0625% Bupivicaine until PCEA pump. PCEA pump 0.0625% bupivacaine at 5-7 cc per hour continuous infusion with a 3cc q 20 minutes demand.
2. LB surgical site infiltration: A single 20mL liposomal bupivacaine vial containing 266mg of free-base bupivacaine will be mixed with 60mL of 0.25% bupivacaine HCl and then diluted in preservative-free sterile 0.9% saline for maximal volume not to exceed 300mL. Dilution with 0.9% saline will be dependent upon length of surgical incision per attached protocol (Appendix E). The solution will be injected using a large bore 22-gauge needle in equal distribution into the peritoneum, along the fascia and into the subcutaneous tissues of the surgical wound by trained faculty surgeons and/or fellows.

All new gyn-onc faculty study team members (none anticipated beyond the 2 new individuals added with this re-submission, Anna Beavis and J Stuart Ferriss) who wish to consent and enroll patients on the randomized trial will need to complete training on LB surgical site infiltration prior to enrolling patients onto the randomized trial as the current study team did as part of the 12 patient pilot on IRB00223229. This training includes both didactic and hands-on learning led by the Pacira. Pacira routinely trains surgeons newly offering surgical site infiltration with LB to their patients and has published their competency training in the peer reviewed literature. Competency is assessed and determined to be satisfactory after didactics as well as following a 3 patient OR observation per surgeon. These pilot patients will be asked to consent for study participation in the same way that the initial 12 pilot patients were on IRB00223229.

All participants will otherwise be enrolled on the standard gyn-oncology ERAS pathway which includes pre-operative education, pre-operative medications, post-operative medications, post-operative fluid management, and mobility and feeding protocols.

Participation will be offered to patients undergoing a planned laparotomy via midline vertical skin incision on the gynecologic oncology service. Patients will be identified from gynecologic oncology pre-operative clinics. Eligible participants will be stratified based on pre-operative likelihood of malignancy (into likely benign disease vs. likely malignant disease). This stratification will be based upon the surgeon's preoperative impression of likelihood of malignancy. Participants will then be randomized 1:1 via a stratified randomized technique that accounts for a binary (yes/no) likelihood of malignancy by the inpatient pharmacy within 48 hours of surgery to the two study arms. Consent for study participation will be reviewed with the patient and signed prior to surgery.
In the rare event a patient enrolled on trial does not proceed with surgery, their slot will not be reallocated in the randomization scheme. Specifically, the inpatient pharmacy will generate random treatment assignments as follows:

1. IDS has randomization list from statistician
2. Randomization is stratified by "suspicion of cancer – Yes or No"
3. Study team will complete Randomization Request form prior to date of surgery and fax to IDS
4. If randomized to liposomal bupivacaine arm,
    a. The authorized prescriber will enter Epic order (which will be modified to reflect the new IRB number)
    b. At time of surgery an OR staff member will call IDS to coordinate pickup/delivery of study drug
5. If randomized to TEA arm,
    a. The study team will notify the anesthesia block team the day before surgery to put the patient on the block list as per existing clinical work-flow for patients planned for pre-procedure blocks.

All participants will be enrolled on the standard gyn-oncology ERAS pathway which includes pre-operative education, pre-operative medications, post-operative medications, post-operative fluid management, and mobility and feeding protocols.
Patients will be considered to be "on study"until collection of VAS pain scores and opioid consumption is complete on postoperative day 14. Each participating individual will have no extra or additional outpatient study visits.
Because of the invasive nature of the interventions, neither the trial participants nor the investigators will be blinded to group allocation.
Visual analog scale (VAS) pain intensity scores will be collected from patients at rest at 6, 12, 18, 24, 30, 36, 42, 48, and 72 hours after surgery and then once daily (at noon ± 4 hours) through postoperative day 14. Subjects will also record an unscheduled pain score immediately before any requested opioid pain medication. The exact time of the assessment will be recorded to limit variability. Total opioid consumption in IV morphine equivalents (mg) during the first 48 hours postoperatively will be tracked for each subject.

Pain scores obtained during the opioid medication-specific window (see table below) will be replaced with the worst observation carried forward (WWOCF). For subjects who take a rescue medication, their VAS pain scores recorded within the window of controlled type of rescue medication will be replaced by the "worst" observation. The worst observation will be the highest VAS score from the end of the previous rescue window or the end of surgery, whichever is later.

Opioid Rescue Medication Window

Medication	**Route**	**Window Used to Impute VAS**
Oxycodone, Oxycocet, Percocet, acetaminophen-oxycodone, Oxycontin	PO, IM, IV, SC	6 hours
Morphine	IV, PO, SC	4 hours
Hydromorphone (Dilaudid), Hydromorphone hydrochloride	IV	2 hours
Hydromorphone (Dilaudid), Hydromorphone hydrochloride	PO, IM, SC	4 hours
Hydrocodone	PO	6 hours
Fentanyl	IV, PO, IM	6 hours
Hydrocodone combination product - Vicodin, Norco, Lorcet, Lortab, hydrocodone-acetaminophen	PO	6 hours
Codeine combination product - Tylenol 3, acetaminophen-coedine, Paracetamol Forte, Tylenol 4	PO	6 hours
Ultram, Tramadol, Tramadol hydrochloride	PO	6 hours

PO = oral, IV = intravenous, IM = Intramuscular, SC = subcutaneous,.

If other rescue medications not listed above are given, the window will be determined post-hoc. If a combination opioid product is given, the window will be determined by the opioid part of the medication.

Patients enrolled on this study will also be asked to complete a daily 15-question patient perceived quality of recovery survey (QoR-15, Appendix A) at noon ± 4 hours during a period of rest up to and including the day of discharge or postoperative day 7 (whichever comes first) in order to obtain longitudinal data about the quality of recovery experienced by patients. Patients unable to complete the questionnaire independently will be asked for verbal responses to each item.
Patients will have biomarkers of surgical stress response measured by blood samples. Blood samples (10mL whole blood) will be collected on the day of surgery when routine IV access is established in preop or the operating room and postoperative days 1 through 7 for analysis of peripheral blood counts, serum glucose, ACTH, epinephrine, total cortisol, ADH, interleukins, ANP, syndecan-1, glycosominoglycans,

CRP and TNF-α. Blood collection on postoperative day 0 is optional. The patient will not be asked to have any additional IV access for blood other than that which would normally be obtained just prior to surgery and daily postoperatively. Serum will be isolated and banked in our scientific collaborator Dr. Shih's lab for ELISA by his research team and the SOM Onc Human Immunology Core. Saliva (1mL) will also be collected by patients between at 6PM preoperatively and postoperative days 0 through 7 (q24±1h) thereafter for cortisol measurement by ELISA since measurements of salivary cortisol more accurately reflect serum free cortisol concentrations than do measurements of serum total cortisol. Saliva collection on postoperative day 0 is optional and is mandatory on postoperative days 1-7. The salivary collection protocol has previously been published [1]. Samples will be banked in Dr. Shih's lab. The feasibility of biospecimen collection, banking and analysis was tested and confirmed during the pilot phase of this project.
Primary and secondary efficacy variables/measures as well as their rationale are described below.
Study drug regimens/administration are described below. TE blocks will be carried out according to the standard institutional protocol. The pharmacy will be responsible for diluting LB according to the length of the surgical incision reported to them by the OR nurse within 4 hours of abdominal wall closure.

In addition, an efficacy interim analysis for the primary outcome will be carried out when 20 patients are enrolled in each group. The results will be provided to the DSMB committee to determine whether one method is truly inferior to the other before enrollment continues (see section on Early stopping rules below). The determination will be based on comparing the average AUC of VAS for 0-48 hours postoperative. Of the two co-primary endpoints, equivalent pain intensity scores is harder to achieve and is the more clinically relevant one. Interim analysis of toxicity, outcome and ongoing scientific investigations will be performed at least annually by the Sidney Kimmel Comprehensive Cancer Center Data Safety Monitoring Board (SKCCC DSMB). The SKCCC DSMB Recommendation letter will state the timeline for the next required review. The SKCCC DSMB will review aspects of this trial that are outlined in the responsibilities section of the Data and Safety Monitoring Board (DSMB) Guidance. If the committee decides that amendments should be made to this trial, recommendations will be made in writing to the Study Principal Investigator. The study team will submit modifications to the IRB within 60 days of receipt from the DSMB. The Associate Director of Clinical Research, will arbitrate any disagreements between the DSMB and the study Principal Investigator. These changes may include early termination of accrual if deemed appropriate. The SKCCC Compliance Monitoring Program will provide external monitoring for JHU-affiliated sites in accordance with SKCCC DSMP (Version 6.0, 02/21/2019). The SMC Subcommittee will determine the level of patient safety risk and level/frequency of monitoring.

b. Study duration and number of study visits required of research participants.

   Patients will be considered to be "on study" for the duration of their inpatient hospitalization and for 14 days postoperatively. Each participating individual will have no extra or additional outpatient study visits.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

   Because of the invasive nature of the interventions, neither the trial participants nor the investigators will be masked to group allocation.

d. Justification of why participants will not receive routine care or will have current therapy stopped.

   "Routine care" is quite varied for laparotomies at our institution, as well as among large volume surgical centers. Thoracic epidural analgesia is standard at some institutions while surgical incision infiltration of bupivacaine or liposomal bupivacaine is the primary modality of pain

control at other institutions. Within the gynecologic oncology division at our institution not all individuals receive an epidural for analgesia based upon surgeon preference therefore this study does not require one arm of patients to receive non-routine care as "standard pain management" has yet to be defined by clinical data.

e. Justification for inclusion of a placebo or non-treatment group.

Not applicable. Both arms will receive a proven modality of post-operative analgesia.

f. Definition of treatment failure or participant removal criteria.

If the patient has been randomized to the TEA arm of the trial and an epidural cannot be placed or cannot be used due to other circumstances (ie. persistent hypotension) the patient will receive the other elements of the ERAS multimodal pain bundle, which is consistent with our current clinical practice. Intention to treat statistical analyses will be used to test the null hypothesis.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

In the rare event a patient enrolled on trial does not proceed with surgery or decides not to participate in the trial preoperatively, their slot will not be reallocated in the randomization scheme. In the event a participant wishes to drop out of the study prematurely postoperatively (ie. declines further blood/saliva collection and/or to fill out surveys), they will be allowed to do so and the data collected during their enrollment period will still be used for analyses unless they submit a formal written objection.

5. Inclusion/Exclusion Criteria

Inclusion:

- Individuals ≥ 18 years of age
- Planned laparotomy by and admitted to the gynecologic oncology service at JHH.

Exclusion:

- Individuals who have a contraindication to thoracic epidural analgesia
    - Individuals with a coagulation disorder
    - Individuals with an infection at the site of epidural placement
    - Individuals with intracranial pathology such as non-communicating increased intracranial pressure or obstruction of cerebrospinal fluid flow related to mass lesions
    - Individuals with spinal pathology: abnormal spine anatomy, surgical fusion, or spinal column lesions
- Individuals who have a contraindication to liposomal bupivacaine
    - Individuals with a known allergic reaction to liposomal bupivacaine
    - Individuals with Childs-Pugh Class B or C liver disease
- Individuals who have a history of long-term opioid use for chronic pain, defined as use of opioid pain medications for ≥4 weeks prior to surgery.

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

Extended-release liposomal bupivacaine (LB) was recently approved by the FDA for single-dose surgical site infiltration to produce postsurgical analgesia. The liposomal preparation consists of microscopic multi-vesicles with a lipid-soluble lining and an aqueous core containing encapsulated bupivacaine allowing it to be slowly released over a period of up to 72–96 h.[14] Existing data

indicate that surgical site infiltration with LB following mammoplasty and open colectomy decreases postoperative opioid requirements and length of stay.[15, 16] Recently, the Mayo Clinic published their experience with abdominal incision injection of LB versus standard bupivacaine hydrochloride after laparotomy for gynecologic malignancies. Compared to bupivacaine hydrochloride, abdominal incision infiltration with LB was associated with less opioid consumption as well as lower rates of postoperative nausea and ileus. A single 20mL liposomal bupivacaine vial containing 266mg of free-base bupivacaine will be mixed with 60mL of 0.25% bupivacaine HCl and then diluted in preservative-free sterile 0.9% saline for maximal volume not to exceed 300mL. Dilution with 0.9% saline will be dependent upon length of surgical incision per attached protocol (Appendix E). The pharmacy will be responsible for diluting the drug according to the length of the surgical incision reported to them by the OR nurse at the start of the case. The solution will be injected using a large bore 22-gauge needle in equal distribution into the peritoneum, along the fascia and into the subcutaneous tissues of the surgical wound by trained faculty surgeons and/or fellows.[17]

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

Not applicable. All medications are FDA approved for their intended use.

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

7. Study Statistics

a. Primary outcome variables:

The study has two co-primary endpoints: (1) the mean Area under the Curve (AUC) of visual analog scale (VAS) pain intensity scores from 0 to 48 hours postoperatively and (2) total opioid consumption (IV morphine equivalents, mg) from 0 to 48 hours postoperatively. The primary hypothesis will be assessed in joint hypothesis testing which controls the type I error at 0.025 across both non-inferiority tests; AUC for VAS pain scores and total opioid consumption through 48 hours postoperatively. Significance will need to be achieved for both co-primary endpoints.

For analyzing the AUC of the VAS pain assessment, we will use an approach that has been previously used in Pacira studies. The area under the curve (AUC) is derived using the trapezoidal rule (see formula below) using the adjusted and imputed VAS pain scores. The VAS scores will be adjusted for the use of rescue medication using the WWOCF approach. AUC will start with the first postsurgical pain assessment. All pain assessments through 48 hours after surgery, including both scheduled and unscheduled will be used in deriving AUC. Exact assessment times will be used in deriving AUC.

$$AUC = \left\{\sum_{i=2}^{n}(p_i + p_{(i-1)})(t_i + t_{(i-1)})\right\}/2$$

The AUC for VAS may be analyzed using ANOVA with treatment group as a main effect and include other covariates as deemed reasonable. Based on the model, the LS Mean and SE will be reported for each treatment group. The 95% confidence interval for the difference between

treatment groups and the one-sided test performed at 2.5% level of significance will be inspected for non-inferiority.
Total opioid consumption over 48 hours postoperatively will be abstracted by our research assistant from the medical administration record (MAR) as it appears in the EMR for each patient.

The analysis of total opioid consumption over 48 hours is based on an approach that has been used previously in Pacira studies. For the endpoint total opioid consumption (IV morphine equivalents, mg) from 0 to 48 hours postoperatively, opioid dose will be converted to IV morphine equivalent dose using the conversion factor from the table below. The endpoint will be the summation of all opioids taken post-surgery through 48 hours. Subjects with no opioid use during the period in question will be assigned a dose of 0 mg for summaries.
The total opioid consumption through 48 may be analyzed using ANCOVA with treatment group as a main effect and include other covariates as deemed reasonable. Based on the model, the LS Mean and SE will be reported for each treatment group. The 95% confidence interval for the difference between treatment groups and the one-sided test performed at 2.5% level of significance will be inspected for non-inferiority. The data may be natural log transformed.

Medication	Unit	Route	IV Morphine Conversion Factor
Duramorph	mcg	IT	0.1
Oxycodone, Oxycocet, Percocet, acetaminophen-oxycodone	mg	PO	0.5
Morphine	mg	IV, IM, SC	1
Morphine	mg	PO	0.33
Hydromorphone (Dilaudid)	mg	IV, IM, SC	6.67
Hydromorphone (Dilaudid)	mg	PO	1.3
Fentanyl	mg	IV, PO, IM	100
Hydrocodone combination product - Vicodin, Norco, Lorcet, Lortab, hydrocodone-acetaminophen, Ketobemidone	mg	PO	0.33
Codeine combination product - Tylenol 3, acetaminophen-coedine, Paracetamol Forte, Tylenol 4	mg	PO	0.05
Ultram, Tramadol, Tramacol hydrochloride	mg	PO, IM	0.08
Demerol, Meperidine, Pethidine	mg	IV, SC	0.1
Demerol, Meperidine, Pethidine	mg	PO	0.033
Ketobemidone, Oxycodone	mg	IV	1

Regarding the non-inferiority margin for the total opioid endpoint, previous literature indicated a difference of 10.6mg IV morphine equivalent dose daily is a clinical different threshold [24]. Therefore, total opioid consumption through 48 hours for LB treatment group is to be no more than 21.2 IV (10.6 x 2 Days) morphine equivalent doses greater than the total opioid consumption through 48 for TEA treatment group. It may be reasonable to apply a natural log transformation, in which case the NIM threshold will be adjusted accordingly.

The study is powered for the primary outcome of Area under the Curve (AUC) for pain from 0-48 hours. From review of the literature of previous studies, we deemed a margin of 80% of 48 hours to be non-inferior [24,25,]. A group sample size of 50 per cohort is needed achieve a 90% power to detect non-inferiority using a one-sided, Mann-Whitney test. The margin of non-inferiority is 38 (80% of 48 hours). The non-inferiority margin corresponds to an increase in pain, not a decrease. The pain VAS ranges from 0 to 10, with 10 being the worst pain. Therefore, non-inferiority will be declared if the average AUC for liposomal bupivacaine is no more than 38 units compared to the average AUC in the TEA group. The true difference between the means is assumed to be 0.0. The significance level (alpha) of the test is 0.025 and the data are drawn from populations with standard deviations of 55.0. These assumptions were derived from previous Pacira studies. It is reasonable to assume that the standard deviation of the AUC for 0-48 hours is about 55 units and the difference between the groups is 0. Sample size calculations were performed using PASS (PASS 16 Power Analysis and Sample Size Software (2018). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass). Of note, with sequential testing of the co-primary endpoints, the study remains to be adequately powered with the addition of the total opioid consumption co-primary endpoint. A sample size of 50 participants in each arm will have adequate power (>90%) to detect non-inferiority with a margin of 21.2 IV morphine equivalents using a one-sided test with a common standard deviation of 25 and alpha of 0.025. The non-inferiority margin was determined by the clinically significant threshold of 10.6 mg in daily IV morphine equivalent dose [24], therefore, 21.2 morphine equivalent dose for over 2 days (0-48 hours).

Intention to treat statistical analyses will be used to test the null hypothesis. Thus, if a patient has been randomized to the TEA arm of the trial and an epidural cannot be placed or cannot be used due to other circumstances (ie. persistent hypotension) the patient will receive the other elements of the ERAS multimodal pain bundle, which is consistent with our current clinical practice and that patient's data will be included in the dataset for the TEA arm in the final analysis. Additionally, in the event a participant wishes to drop out of the study prematurely postoperatively (ie. declines further blood/saliva collection and/or to fill out surveys), they will be allowed to do so and the data collected during their enrollment period will still be included in the dataset for their respective treatment arm unless they submit a formal written objection.

Secondary outcome variables:

T-tests or the nonparametric Mann-Whitney test will be used to compare normally and non-normally distributed data between the study arms. The log-rank test will be used to compare the time to (ROBF) as well as the time to postoperative diuresis to account for right censoring in which case no event (ROBF/diuresis) is observed within the observed time. A Poisson regression model will be used to compare the length of hospital stay. Chi-square tests will be used to compare the incidence of major postoperative complications between the two treatments. Chi-square tests will also be used to compare the incidence of major postoperative complications between the two treatments. Daily mean and median as well as mean baseline change in surgical stress biomarkers will be compared between treatment groups using t-tests or the Mann-Whitney test depending on whether data are normally or non-normally distributed. Average daily QoR-15 scores will be compared between the study cohorts.

b. Early stopping rules.

If there is concern for harm on either arm of the study this will be immediately discussed with the PI and the study will be stopped until the concern is resolved. The PI will internally monitor the progress of the trial, including review and confirmation of all safety/treatment-related outcomes, response assessments, safety reports and/or any related source documentation. As per above, the DSMB will meet after 20 patients have been enrolled in each arm. Regarding the futility boundary for the interim analysis – based on the results from the pilot study in 2019, the pain for the Epidural group and for the Exparel group are about the same (3.9 vs 4.0 in a 0-10 scale). With the O'Brien-Fleming futility boundary of 0.2986, there is only 0.1% chance of falsely crossing the futility boundary and stopping the study at 20 participants per arm assuming equal pain for both groups. The overall power remains to be over 90%. If in case that the Exparel group is truly inferior to the Epidural group by at least the pre-specified non-inferiority margin, there is at least a 38% chance of claiming early futility at 20 patients per arm to protect more patients from being exposed to the inferior treatment.

Interim analysis of toxicity, outcome and ongoing scientific investigations will be performed at least annually by the Sidney Kimmel Comprehensive Cancer Center Data Safety Monitoring Board (SKCCC DSMB). The SKCCC DSMB Recommendation letter will state the timeline for the next required review. The SKCCC DSMB will review aspects of this trial that are outlined in the responsibilities section of the Data and Safety Monitoring Board (DSMB) Guidance. If the committee decides that amendments should be made to this trial, recommendations will be made in writing to the Study Principal Investigator. The study team will submit modifications to the IRB within 60 days of receipt from the DSMB. The Associate Director of Clinical Research, will arbitrate any disagreements between the DSMB and the study Principal Investigator. These changes may include early termination of accrual if deemed appropriate. The SKCCC Compliance Monitoring Program will provide external monitoring for JHU-affiliated sites in accordance with SKCCC DSMP (Version 6.0, 02/21/2019). The SMC Subcommittee will determine the level of patient safety risk and level/frequency of monitoring.

1. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency. The risks listed for liposomal bupivacaine surgical site infiltration and for thoracic epidural here and on the study consent are the same ones listed for patients on the 9/18 version of the Consent for Anesthesia and Anesthesia-Related Procedures that is routinely used for surgery here at Johns Hopkins for Regional Nerve Block and for Epidural Anesthesia, respectively.

- Liposomal bupivacaine surgical site infiltration: Infection, soreness, bruising, weakness, persistent numbness or pain, injury to blood vessels or nerves, and, rarely, seizures or loss of consciousness.
- Thoracic Epidural Analgesia: Headache or backache; infection; ringing in the ears; persistent or permanent weakness; numbness or pain; loss of sensation or other nerve functions, changes in my heart rate or blood pressure, and rarely paralysis or seizures.

b. Steps taken to minimize the risks.

- All TEA will be placed per institutional standard protocols.
- All liposomal bupivacaine infiltration will be performed as outlined in the wound infiltration protocol (provided in supplemental materials)
- As noted above, all surgical stress biomarkers obtained through blood draws will be drawn at already planned IV access for standard surgical care therefore no additional IV access for blood will be obtained.
- All adverse events will be monitored by the PI and logged in the adverse event log. Adverse event definitions and severity have been defined prior to trial initiation.

c. Plan for reporting unanticipated problems or study deviations.

All unanticipated problems or study deviations will be brought to the immediate attention of the PI. Study team research meetings, which will occur monthly during the duration of this study, will be used to further troubleshoot study deviations, problems or concerns raised by co-investigators. The PI will oversee all data and safety monitoring. The PI will internally monitor the progress of the trial, including review and confirmation of all safety/treatment-related outcomes, response assessments, safety reports and/or any related source documentation. The data and safety monitoring plan entails that the PI submit all safety and problem/event information to the IRB on a semi-annual basis. Further, as noted above, the DSMB will meet after 20 patients have been enrolled in each arm. Interim analysis of toxicity, outcome and ongoing scientific investigations will be performed at least annually by the Sidney Kimmel Comprehensive Cancer Center Data Safety Monitoring Board (SKCCC DSMB). The SKCCC DSMB Recommendation letter will state the timeline for the next required review. The SKCCC DSMB will review aspects of this trial that are outlined in the responsibilities section of the Data and Safety Monitoring Board (DSMB) Guidance. If the committee decides that amendments should be made to this trial, recommendations will be made in writing to the Study Principal Investigator. The study team will submit modifications to the IRB within 60 days of receipt from the DSMB. The Associate Director of Clinical Research, will arbitrate any disagreements between the DSMB and the study Principal Investigator. These changes may include early termination of accrual if deemed appropriate. The SKCCC Compliance Monitoring Program will provide external monitoring for JHU-affiliated sites in accordance with SKCCC DSMP (Version 6.0, 02/21/2019). The SMC Subcommittee will determine the level of patient safety risk and level/frequency of monitoring.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

CRFs will be organized in a binder for each patient participant. The binder will follow the patient with their inpatient chart throughout their perioperative journey. At the time of hospital discharge, the each CRF binder will be stored in a locked filing cabinet in the PI's office. Post-operative pain medication logs collected from patients in the outpatient setting at their first postoperative appointment will be given to the PI to file with the other CRFs in the patient's binder. All patient data will then be entered into a secure, password protected REDCaP database housed on a JHED-enabled computer and only those listed as investigators on this study will have access to this database to minimize the risk of breaches of confidentiality.

e. Financial risks to the participants.

There is no anticipated financial risk to the participants. Liposomal bupivacaine and surgical stress biomarker assays will be paid for by the study and will not be a cost to the individuals participating. There is no anticipated burden of extra cost to patients beyond what industry funding and standard perioperative care provide.

2. Benefits

a. Description of the probable benefits for the participant and for society.

This study would be the first randomized trial comparing the value of the two prevailing modalities of loco-regional analgesia (TEA and LB surgical site infiltration) used by ERAS programs for open abdominal surgery in the U.S. The proposed value analysis is unique in accounting for a wide spectrum of quality, outcome and cost variables. Further, it has potential to set a precedent for quantifying the impact of discrete ERAS components on the surgical stress response. While the concept and theory behind surgical stress are old, little is known about its pathophysiology in the era of modern surgery. Results from this study would also better define the optimal non-opioid pain management regimen for patients recovering from

open abdominal surgery and are urgently needed by the American College of Surgeons and the Society of Gynecologic Oncology in formulating our national ERAS guidelines.

3. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Patients will be not be given any payment or compensation for participating in this study.

4. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

Cost of liposomal bupivacaine for surgical site infiltration has been estimated at $40,000 (cost of drug plus pharmacy costs) and surgical stress response biomarker collection and analysis (translational endpoint) has been estimated at $20,000. The principle investigator has received for industry funding for the trial. Again, there is no anticipated burden of extra cost to patients beyond what industry funding and standard perioperative care provide.

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