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Wound Infiltration with Liposomal Bupivacaine with or without Intrathecal Analgesia in Laparotomy for Gynecological Malignancy: A Randomized Controlled Trial

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Wound Infiltration with liposomal bupivacaine with or without intrathecal analgesia in laparotomy for gynecological malignancy: A Randomized Controlled Trial

Principal Investigator: **Sean C. Dowdy, M.D.**

Co-Investigators: **Katherine W. Arendt, M.D.**

Christopher J. Jankowski, M.D., M.B.O.E.

Deepa Maheswari Narasimhulu, M.B.B.S.

Michelle A. Ochs Kinney, M.D.

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A. Background:

Enhanced recovery after surgery (ERAS) has become the standard of care for patients undergoing surgery for gynecological malignancies after the ERAS guidelines for gynecologic oncology were widely disseminated in 2016.[1,2] Regional analgesia can be a part of a multimodal analgesic regimen leading to opioid-sparing effects.[3] While epidurals are effective for pain control, they may slow postoperative mobility, delay return of bowel function, prolong the need for urinary catheters, result in transient hypotension, and may be ineffective in as many as 50% of patients.[4, 5] Alternate opioid sparing modalities include intrathecal analgesia and incisional local anesthetic infiltration.

Intrathecal analgesia (ITA) has been shown to shorten time to return of bowel function and length of hospital stay when compared to epidural analgesia.[5] Intrathecal analgesia is known to be effective after cesarean delivery;[6] preservative free morphine in a dose of 100 to 200µg is the most commonly used agent. Following a national shortage of preservative-free morphine, intrathecal hydromorphone has been explored as a potential alternative for postoperative analgesia. Hydromorphone is more lipophilic than morphine which may allow for a favorable side effect profile.[7, 8] Intrathecal analgesia is being incorporated into ERAS protocols to decrease postoperative opioid consumption.

In our practice, wound infiltration with liposomal bupivacaine is the cornerstone of treatment of early postoperative pain within our ERAS pathway, and resulted in a reduction in patient-controlled analgesia from 33.35 to 4.1% (P<.001) in patients undergoing laparotomy and complex cytoreduction for ovarian cancer.[9] The advantages of wound infiltration are that it is quick, simple, inexpensive, and consistently effective. Intrathecal analgesia is currently used in less than 1% of our patients.

Given that visceral pain which can be significant in tumor debulking is not targeted by incisional bupivacaine, combining ITA with incisional liposomal bupivacaine (ILB) to provide more intensive pain relief in the first 24 hours is a viable option. However, it is unclear if patient experience with pain management is improved with ITA given that opioid related side effects (nausea, vomiting, itching) as well as rare adverse events related to spinal injections (postural puncture headache) can occur. Additionally, ITA is invasive and expensive. The purpose of this investigation is to evaluate whether ILB is non-inferior to a combination of ITA and ILB for management of postoperative pain after laparotomy for gynecological malignancy within an established enhanced recovery pathway using the Overall Benefit of Analgesia Score (OBAS) as our primary outcome[10]. Additionally, we will evaluate cumulative 24 hour postoperative morphine milligram equivalents (MME) consumption, pain scores, length of stay, cost, and patient satisfaction as secondary outcomes.

B. Hypothesis and Aims

Hypothesis: Among women undergoing laparotomy for gynecological malignancy, the pain experience (as measured by the OBAS) of those randomized to no additional intervention will be non-inferior to

that of patients randomized to ITA with 150mcg of hydromorphone within an established enhanced recovery pathway which includes incisional ILB (in both arms).

Specific Aims

1. Evaluate if no additional intervention is noninferior to ITA for postoperative pain experience 24 hours after surgery after laparotomy for gynecological malignancy within an established enhanced recovery pathway which includes ILB.
2. Evaluate the effect of intrathecal analgesia on patient satisfaction with postoperative analgesia after laparotomy for gynecological malignancy.
3. Report the impact of ITA use on cost.
4. Validate the QOR-15 in our population

C. Research plan and methods:

C.1 Study design: Randomized controlled study

Randomization:
1. Stratified by:
    a. Likelihood of bowel resection ≥50% or <50% as assessed by surgeon
    b. Planning to use NSAIDs vs not planning to use NSAIDs
2. Allocation ratio- 1:1
3. Allocation sequence- permutated bock randomization with varying block sizes (Provided by statistician in the Department of Biostatistics and Informatics)

Blinding: None
Allocation concealment method: web-based

C.2 Population, intervention, comparator, and outcomes

Population:
Women undergoing laparotomy for gynecological malignancy
Inclusion: age >18yo and ≤80yo, elective surgery for suspected (based on consulting surgeon's opinion- imaging, lab, path) gynecological malignancy, ERAS protocol
Exclusion:
1. Inability to read or understand English
2. Prehospitalization narcotic use if weekly average daily oral morphine equivalent of >20 mg.
3. Chronic pain syndromes such as fibromyalgia.
4. Extensive surgery planned (surrogate for postop pain): Planned ICU admission, abdominoperineal resection, exenteration, use of IORT, HIPEC
5. Contraindication to neuraxial analgesia:
    a. Coagulopathy
        i. INR >1.2 Current or predicted after surgery (e.g. planned right hepatic resection)
        ii. Thrombocytopenia. plts <100.
        iii. Hemophiliac disease states (hemophilia, von Willebrand disease, etc.)

iv. Patients receiving antithrombotic or thrombolytic therapy are excluded according to the ASRA guidelines (Reference: https://rapm.bmj.com/content/rapm/43/3/263.full.pdf)

b. Localized infection at the potential site of injection
c. Significant developmental or structural spinal abnormalities that would preclude a safe spinal technique. These include spina bifida, tethered spinal cord, lumbar spinal fusion, and active lumbar radiculopathy.

6. Patients with stage 4 or 5 kidney disease (GFR less than 30 ml/min per 1.73 m2).
7. Intolerance or allergy to opioids, acetaminophen, or amide-type local anesthetics
8. Current pregnancy

Intervention: ITA with 150mcg of hydromorphone in addition to ILB. For patients randomized to ITA, injection will be performed in the O.R.

Comparator: ILB

Standardized perioperative anesthetic protocol (Appendix A) and postoperative protocol (Appendix B) will be used

Outcomes:

Primary outcome:

Overall Benefit of Analgesia Score (OBAS): The OBAS will be administered in the form of a questionnaire to be filled out by the participants at baseline (preoperatively) and at 24 hours (±2 hours) postoperatively. The OBAS consists of 7 items that assess pain intensity, opioid-related adverse effects and patient satisfaction with pain management. The composite score ranges from 0 (best) to 28 (worst).

Secondary outcome:

Cumulative 24 hour narcotic consumption, measured in morphine metabolic equivalents (MME)
Postoperative pain scores (rest, movement) at 4, 8, 16 and 24 hours after surgery.
Time to first analgesic request
Use of intravenous patient-controlled analgesia
Use of IV rescue opioids
Length of stay
Fluid balance: Additional fluid requirement after 24 hours of surgery, weight gain following surgery
Cost of care

Adverse events:

Related to spinal injection: Puncture site bleeding/hematoma/infection; Spinal headache
Related to systemic opioid effects: Itching; Nausea/vomiting; Sedation; respiratory depression
Related to delayed recovery: Time to regular diet/Bowel movement, postoperative ileus, time to first ambulation, time to Foley removal, voiding dysfunction/ need for re-catheterization, readiness for discharge

Cost analysis:

OR time and surgical time
Total and pain management related standardized costs

Exploratory end point:
QoR 15[11]: The QoR 15 will be administered in the form of a questionnaire to be filled out by the participants at 24 hours (±2 hours) postoperatively for the purposes of validation.

Sample size calculation

The primary outcome will be the mean OBAS score measured at 24 hours postoperative. Using a non-inferiority margin of +3 points, SD of 5, power of 90%, and 1-sided two-sample equal variance t-test with an alpha of 0.05, the sample size is 49 participants per group, 98 participants total. If it is determined after randomization that a participant will need an additional spinal injection, they will be evaluated for data. We will perform intention-to-treat analysis including these participants as well as per-protocol analysis excluding them. Based on our data, this would be a rare situation as <1% of our current patients need a spinal. The sample size will be increased by 5% to maintain power for the per-protocol analysis. Increasing the sample size by 5% changes the sample size to 52 subjects per arm, for a total of 104 subjects.

We will pilot the OBAS in our target population (20 patients) in order to obtain an estimate of the SD specific to our patient population. The SD reported in the literature varies from 2 to 4, so we used an SD of 5 in our calculation in order to be conservative. A SD of 4 would require 32 patients per group. Prior to the enrollment of the first patient in this trial, a modification will be submitted to the institutional review board if the pilot data prompts us to modify sample size.

Statistical analysis plan

Data will be summarized using standard descriptive statistics by reporting mean (SD) or median (IQR) for continuous variables and frequency and percentages for categorical variables. Continuous variables will be compared between the two treatment arms using the two-sample t-test or the Wilcoxon rank sum test as appropriate. Categorical variables will be compared between the two treatment arms using the chi-square test or the Fisher's exact test. For the primary outcome, the mean OBAS score between the two groups will be presented along with the upper limit of the 95% confidence bound for the mean difference. We will conclude non-inferiority if this upper limit is less than the predefined limit for non-inferiority. Multivariable regression models will be fit to assess for differences in outcomes if there are unbalanced baseline covariates in the two treatment arms.

The primary analysis will be restricted to per-protocol patients and will mirror that of the POP-UP trial, which was a non-inferiority trial that evaluated the effectiveness of continuous wound infiltration in patients undergoing hepato-pancreato-biliary surgery.[12] An intention-to-treat analysis will be performed as a secondary analysis based on the rationale that such an analysis in a non-inferiority trial might introduce bias to no difference.

A thorough review of the data for inconsistencies and outliers will be performed by the statistical team prior to the formal analysis. Data issues will be resolved by the primary investigator and study coordinator. The extent of missing data will be examined and sensitivity analyses of the primary and secondary outcomes will be conducted using multiple imputation if warranted. All statistical analyses will be performed using SAS or R.

Appendix A: Standardized perioperative anesthetic protocol

Preoperatively:

1. Tylenol 1000 mg po, Celebrex 200 mg po.
2. No gabapentin administration unless patient is chronically preoperatively receiving medication. In such a scenario, the patient would take their normal gabapentin dose the morning of surgery
3. Scopolamine patches for patients at high risk for postoperative nausea and vomiting, oral caffeine for headache prophylaxis in caffeine users, and midazolam for anxiolysis can be administered at the anesthesiologist's discretion.
4. For those patients who will receive an intrathecal opioid (150 mcg of hydromorphone), midazolam and fentanyl may be administered for procedural sedation.

Intraoperatively:

1. The anesthetic will include induction with propofol and either succinylcholine or a non-depolarizing muscle relaxant. Maintenance will include volatile anesthetic/air/oxygen. A background propofol infusion may be administered for postoperative nausea and vomiting prophylaxis at the anesthesiologist's discretion.
2. No dexmedetomidine, lidocaine, ketamine or remifentanil infusions.
3. Intravenous fentanyl will be administered by the anesthesia team per the discretion of the anesthesiologist with a goal of no more than 500mcg fentanyl throughout the case.
4. Postoperative nausea prophylaxis with 8 mg of IV dexamethasone, 4 mg of ondansetron, 0.625 mg of droperidol, Ketamine 10 mg IV at the beginning and at the end of the case.
5. Ketorolac 15 mg IV may be given if stratified to "plan for NSAID use"at the anesthesiologist's discretion.

Postoperatively in the PACU:

1. Fentanyl orders in the PACU: 25 mcg IV Q 2minutes prn pain 4 or greater up to 100 mcg maximum. If max dose of fentanyl is reached, discontinue fentanyl and give intravenous hydromorphone. Hydromorphone0.2 mg Q 5 minutes IV prn pain score 4-10 up to 2 mg maximum.
2. If maximum opioids are reached in the PACU, further opioid prescribing is per the discretion of the anesthesiologist.
3. Ketamine 10 mg IV may be given prn breakthrough pain at the anesthesiologist's discretion.
4. Rescue antiemetics, droperidol, Zofran, Kytril at the anesthesiologist's discretion.

5. Caffeine 250 mg IV will only be given at the anesthesiologist's discretion.
6. Ditropan: 5 mg po once as needed for bladder spasms
7. Demerol: 12.5 mg IV Q 15 min prn shivering up to 2 doses maximum.
8. Acetaminophen 1000 mg IV or po, if 6 or more hours have passed since the preoperative dose.
9. Ketorolac 15 mg IV may be given if stratified to "plan for NSAID use"at the anesthesiologist's discretion if it was not previously given in the OR.

Appendix B. Postoperative pain Management

1. Tylenol 1000mg po every 6 hours
2. Ketorolac 15 mg IV every 6 hours X 4 doses if stratified to "plan for NSAID use"
3. Ibuprofen every 6 hours if stratified to "plan for NSAID use", start 6 hours after the last Ketorolac dose. See table below for dose.

Ibuprofen dose	Weight <50 kg	Weight 50-80 kg	Weight >80 kg
Age <65	200	600	800 q 8 hours
Age >65	200	400	600

4. Oxycodone 5mg every 4 hours PRN for moderate pain or pain score of 4-6/10. Administer if pain is unrelieved by Tylenol. For patients who received intrathecal analgesia, start 24 hours after intrathecal dose was given.
5. Oxycodone 10mg every 4 hours PRN for severe pain or pain score of 7-10/10. Administer if pain is unrelieved by Tylenol. For patients that received intrathecal analgesia, start 24 hours after intrathecal dose was given.
6. Dilaudid 0.4mg IV every 2 hours PRN for breakthrough pain. To be given if pain is unrelieved 30 minutes after PRN oral medication is used; if unable to take oral pain meds; or if pain is greater than or equal to 7, use instead of oral pain medication.
7. Oral intake, timing of Foley catheter removal and ambulation in accordance to ERAS protocol and discretion of the surgeon.

Appendix C: OBAS questionnaire

Appendix D: QoR 15 questionnaire

Abbreviations:

ERAS: Enhanced recovery after surgery
ITA: Intrathecal analgesia
ILB : Incisional liposomal bupivacaine
MME: Morphine milligram equivalents
OBAS : Overall Benefit of Analgesia Score

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