A randomized-controlled trial comparing liposomal bupivacaine, plain bupivacaine, and the mixture of liposomal bupivacaine and plain bupivacaine in transversus abdominus plane block for postoperative analgesia for open abdominal hysterectomies

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HENRY FORD HEALTH SYSTEM IRB PROTOCOL FORMAT

Appendix 1

(Incomplete applications will be returned, & inadequate responses may lead to a delay in review.)You may mark your responses in the shaded areas following each question. Supporting documents (articles, drug toxicity information, etc.) must be submitted when applicable. A "See Attached" response will not be accepted for review. Be concise & clear.

Directions:

Sponsored protocol: If you have a sponsored protocol (e.g., pharmaceutical), a grant application (e.g., National Institutes of Health), or another peer-reviewed protocol, you may submit that protocol/application along with the application elements. It is the responsibility of the Principal Investigator to assure, however, that the protocol/application contains the information requested in this "IRB Protocol Format". Additional sheets should be attached to the protocol/application as necessary to provide the information (e.g., a description of the process of consent) required for IRB review. When available, the Investigator's Brochure must be submitted along with the research protocol, or a summary of the preclinical/animal data and any relevant clinical data.

Physician Initiated protocol: If you have not been provided a protocol from an outside source, you must develop one. The following is the "Henry Ford Health System "IRB Protocol Format".

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1. PURPOSE: State in one or two sentences the purpose or objective of this project. The goal of this study is to evaluate the effectiveness of different formulations of bupivacaine infiltrated into the transversus abdominis plane (TAP) on post-operative pain management after open abdominal hysterectomy.

2. SPECIFIC AIMS: Number your aims so that the aims can be referred to in the Project Design and Data Analysis sections of this outline. 1) To determine if a TAP block with liposomal bupivacaine provides effective post-operative analgesia after open abdominal hysterectomy. 2) To determine if the mixing of liposomal bupivacaine with bupivacaine hydrochloride provides improved analgesia as compared to either drug alone when used for a TAP block.

3. RATIONALE FOR THE PROJECT:
   a. State the rationale for the project and support it with background information about the project. Critically evaluate existing knowledge, and specifically identify the gaps in knowledge the project will fill. Liposomal bupivacaine is a novel formulation of the local anesthetic bupivacaine in which the drug is encapsulated and slowly released over time up until 72 hours post-injection Since liposomal bupivacaine is slow-released, liposomal bupivacaine may provide delayed post-operative analgesia. Bupivacaine hydrochloride typically provides 24-48 hours of analgesia. We hypothesize that the combination of liposomal bupivacaine to bupivacaine hydrochloride will provide superior analgesia both immediately and up to 72 hours post-operatively. Liposomal bupivacaine was initially FDA approved for surgical site infiltration and has been recently FDA approved for infiltration in the transversus abdominus plane. TAP blocks are routinely used as a part of multimodal analgesia to decrease pain scores and decrease opioid consumption after abdominal surgery. Liposomal bupivacaine infiltrated into the TAP plane has been shown to be effective for post-operative analgesia after robotic prostatectomy, laparoscopic colorectal surgery, and abdominal hernia repair; however, those studies did not compare the effectiveness of liposomal bupivacaine to bupivacaine hydrochloride or to the mixture of Liposomal Bupivicaine and Bupivicaine HCL. Our experience at Henry Ford Hospital suggests that TAP blocks with liposomal bupivacaine provides similar analgesia as those with bupivacaine hydrochloride. This year, a randomized controlled single blinded study comparing liposomal bupivacaine to bupivacaine hydrochloride for TAP blocks for patients undergoing laparoscopic assisted donor nephrectomy showed no difference in pain scores or opioid consumption within the first 48 hours post-operatively. Opioid consumption was slightly decreased 48-72 hours post-operatively in the liposomal bupivacaine group.
   b. State the applicant's prior research and experience in this research area. As a quality improvement initiative, we have retrospectively reviewed the effectiveness of TAP blocks with liposomal bupivacaine and bupivacaine hydrochloride for post-operative analgesia after laparoscopic asissted colectomy and open abdominal hysterectomy. As members of the regional anesthesia division, we have extensive experience performing TAP blocks for a wide range of abdominal surgical procedures.

4. SIGNIFICANCE: State concisely the importance of this project by relating the purpose to broader, long-range objectives. Providing optimal post-operative analgesia to our patients is important to improve

patient satisfaction, decrease opioid related side effects, and promote early recovery and discharge from the hospital. This study will help determine if using liposomal bupivacaine alone or in combination with bupivacaine hydrochloride provides enhanced post-operative analgesia.

5. SUBJECTS IN THE PROJECT:
   a. State the inclusion and exclusion criteria for enrollment of subjects. Inclusion criteria: elective open abdominal hysterectomy with a midline incision, age>18, ASA 1-3. Exclusion criteria: patient with a chronic pain condition, major unexpected surgical complication, unexpected prolonged intubation, patient refusal, local anesthetic allergy, any contraindication to regional anesthesia, and greater than two attempts for TAP block by residents and greater than one attempt by staff anesthesiologist.
   b. Describe the control population (if utilized) and justify its selection.Our current standard practice is to use 0.25% bupivacaine for TAP blocks, therefore, the control population is the group receiving 0.25% Bupivacaine.
   c. Support the likelihood of recruiting the number of subjects required to complete the project. Relate this to other projects recruiting similar subjects.We estimate that 100-150 patients undergo open abdominal hysterectomy with a midline incision at Henry Ford Hospital each year. We anticipate an 80% or higher recruitment rate. Therefore, we anticipate recruiting 90 patients within a year. No other studies are recruiting similar patients.

6. PROJECT DESIGN AND PROTOCOL:
   a. Describe the experimental design/methodology.Prospective randomized observer-blinded controlled study.
   b. Outline the protocol, corresponding it to the specific aims; identify the data or endpoints to be analyzed to reach the specific aims. All eligible patients will be seen in the pre-operative holding area to discuss the study. Informed consent will be obtained at that time. The patient will be randomized to one of three groups by random envelope selection. Group 1 will receive a TAP block with a total of 60 mL 0.25% bupivacaine hydrochloride. Group 2 will receive a TAP block with a total of 20 mL of liposomal bupivacaine and 40 mL normal saline. Group 3 will receive a TAP block with a total of 20 mL of liposomal bupivacaine and 40 mL 0.25% bupivacaine hydrochloride. Our standard sedation protocol for all patients receiving any nerve block is to provide a maximum of 2 mg midazolam and 100 mcg fentanyl during procedure. The patient will be monitored per our routine practice standards. The patients will undergo the surgical procedure with general anesthesia as directed by the attending anesthesiologist. All patients will receive 30 mg ketoralac IV. If ketoralac is contraindication, the patient will receive 1000 mg acetaminophen IV. The patient will be recovered and receive routine post-operative care. Patients will be assessed immediately post-operatively in the post-anesthesia care unit (PACU), and one time during each of the following time periods: 0-24 hrs post-operatively, 25-48 hours post-operatively, and 49-72 hours post-operatively. Primary outcomes are total opioid consumption, time to the first opioid administration, and pain score during the above mentioned time periods. Secondary outcomes are patient satisfaction, length of stay in hospital, timing of ambulation, presence of nausea and vomiting, evidence of local anesthetic toxicity and any postoperative hemodynamic instability.
   c. Discuss potential limitations and difficulties in the protocol.We don't anticipate any difficulties with this protocol since patients typically receive a TAP block for post-operative analgesia for open abdominal hysterectomy at Henry Ford Hospital. One limitation of our protocol is that it is not double-blinded. Liposomal bupivacaine is white and distinctive from bupivacaine hydrochloride. Therefore, the anesthesiologist performing the block cannot be blinded to group selection. All other care team members including anesthesia team, surgical team, and floor nurses, will be blinded to the group selection.
   d. Provide a tentative schedule for conducting and completing this project and, if applicable, the multicenter study.We anticipate one year to recruit patients and collect data. Data analysis will take a few months after study completion.
   e. Data collection: Submit a copy of the data collection tool or list the data fields to be collected (review IRB policy, Access to Medical Records for Research).Age, ASA classification, height, weight, BMI, indication for hysterectomy, surgeon, duration of surgery, time of TAP block, time to first break-through analgesic, cumulative analgesic doses and pain scores at rest and with movement in PACU and in the following time periods: 0-24 horus, 25-48 hours, 49-72 hours. in 6 hr increments for the first 24hrs,then every 12 hrs for the next 24 hours. Satisfaction (ie not satisfied, satisfied, very satisfied), length of stay in the hospital, presence of ambulation, presence of nausea and vomiting, evidence of local anesthetic toxicity, presence of hypotension.

7. DATA ANALYSIS: Describe the analysis of the data and relate this to the specific aims in detail. Case reports and medical record reviews also require a description of the planned data analysis (ie. descriptive, observational). The Committee recommends free consultation with the Division of Biostatistics and Research Epidemiology before IRB submission. Many clinical measurements will be recorded post operation. Some are one-time measurements such as total opioid consumption, and some are repeated measurements such as pain scores. Total 8-9 measuring times for those

repeated outcomes. Ideally these time points are at baseline, 6 hours, 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 60 hours and 72 hours. Continuous variables will be summarized with n, mean, standard deviation and range. Frequency counts and percentage will be provided for categorical data. Estimates for averages and proportions will also include 95 % confidence intervals. One-way Analysis of Variance(ANOVA) will be used to assess the efficacy of three anesthetic bupivacaine formulas (G1: bupivacaine HCL; G2: liposomal bupivacaine ; G3: liposomal bupivacaine + bupivacaine HCL) on total opioid consumption, patient satisfaction, length of stay in hospital as well as timing of ambulation. Generalized Estimating Equations (GEE) will be utilized to evaluate the effects of these three anesthetic formulas on repeated measures of pain scores, presence of nausea and vomiting, evidence of local anesthetic toxicity and any postoperative hemodynamic instability. Cox proportion hazard models will be applied to assess the effect of these anesthetic formulas on the time to first opioid administration. The statistical analysis will be obtained by using SAS 9.4 and the tests are claimed to be significant if the p- values are less than 0.05.

8. JUSTIFICATION FOR NUMBER OF SUBJECTS OR DATA:

   a. State the number of subjects or data points to be analyzed in the project at this institution and the total number for multicenter studies. The Committee recommends consultation with the Division of Biostatistics and Research Epidemiology (313) 874-6360. Total 90 subjects are expected given at least 80% recruitment rate of total 100-150 patients undergo open abdominal hysterectomy at Henry Ford Hospital each year.
   b. Describe the statistical justification for this number of subjects or data points.Total 90 patients (30 for each of these 3 groups) will have 80% power to detect the effect size of 0.33 by using One- Way ANOVA for assessing the effects of three formulas on total opioid consumption; and an effect size of 0.24 can be detected with 80% power assuming 0.5 correlation among repeated measures by using repeated One - Way ANOVA for assessing the effects of three formulas on pain scores.

FORM A

HENRY FORD HEALTH SYSTEM (IRB) DRUG/SUBSTANCE INFORMATION

(This form must be completed for each individual drug or substance -investigational or marketed- that is being administered as part of this research study)

1. Generic/Chemical Name: Liposomal Bupivacaine	2. Trade Name: Exparel
3. Manufacturer: Pacira Pharmaceuticals	4. Mode of Administration: other: infiltrated into the transversus abdominus plane
5. How Supplied (dose form & strength): 20 ML vials containing 266 mg liposomal bupivacaine.	6. Who will be administer the drug/substance? Staff anesthesiologist and resident anesthetist
7. Dosage and Schedule Proposed:Groups 2 and 3 will receive 20 mL liposomal bupivacaine as a one time injection for a TAP block.	
8. Will you be utilizing research pharmacy for storage or dispensing of any medication? (if this is an inpatient study, you are required to use research pharmacy). ☐ Yes ☒ No	
9. Describe the primary actions of the drug/substance:Sodium channel blocker that acts to block neuronal impulses.	