Official Title: Extended Release Local Anesthetic for Postsurgical Pain After Posterior Colporrhaphy and Perineorrhaphy: A Randomized Controlled Study

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STUDY OBJECTIVES

Primary Objective

To evaluate the effect of intraoperative infiltration of liposomal bupivacaine at the time of posterior colporrhaphy and perineorrhaphy on postsurgical pain scores during the first 72 hours after surgery as measured by visual analog scales (VAS).

Secondary Objectives

1. To evaluate total opioid consumption during the first 72 postoperative hours, measured in milligram morphine equivalents (MME).
2. To evaluate patient satisfaction with postoperative analgesia as measured by Likert Scales.
3. To evaluate median time to first opioid administration postoperatively.
4. To evaluate hospital length of stay in hours.
5. To evaluate length of stay in post-anesthesia care unit (PACU) in minutes.
6. To evaluate total hospital costs.
7. To evaluate time to first bowel movement postoperatively.
8. To evaluate rate of postoperative nausea and vomiting by antiemetic requirements postoperatively.
9. To evaluate time to successful voiding trial.
10. To evaluate proportion of patients discharged home with a Foley catheter (i.e. failed voiding trials).

BACKGROUND

Liposomal bupivacaine (Exparel; Pacira Pharmaceuticals, San Diego, CA) is an extended release local anesthetic approved by the Food and Drug Administration since 2011 for the treatment of postsurgical pain[1]. It is a multivesicular liposomal delivery system, consisting of a liquid bupivacaine core encapsulated by a phospholipid shell[2]. This delivery technology allows for the slow, sustained release of bupivacaine over at least 72 hours compared to 7 hours with standard bupivacaine[2,3] with plasma levels peaking between 24 and 48 hours[2]. Liposomal bupivacaine has been studied extensively in the general surgery and orthopedic surgery literature[4,5]. Specifically, infiltration of liposomal bupivacaine after excisional hemorrhoidectomy has been shown to significantly lower postsurgical pain scores, decrease total postoperative opioid consumption, increase the number of patients who do not require any opioids, meaningfully delay the median time to first opioid use, and improve patient satisfaction with overall perioperative analgesia[6,7]. In gynecologic surgery, transversus abdominis plane blocks with liposomal bupivacaine in patients undergoing robotic hysterectomy have demonstrated a greater than 50 percent reduction in total opioid use during the first 72 postsurgical hours, while decreasing maximum pain scores when compared to blocks with standard bupivacaine[8]. Studies investigating the use of liposomal bupivacaine in pelvic reconstructive surgery patients are lacking. A randomized controlled trial involving over 100 patients comparing infiltration of liposomal bupivacaine versus placebo after retropubic tension free vaginal tape midurethral sling placement revealed lower pain scores and reduced narcotic use during the first three postoperative days without an

increase in adverse events and with unaffected patient satisfaction[3]. As the female patient population ages, the number of women presenting for pelvic reconstructive surgery is estimated to increase by nearly 50 percent by the year 2050[9]. In this setting, it becomes increasingly imperative to develop evidence-based perioperative care and analgesia regimens to help patients return to their baseline health and functional status after surgery. Posterior colporrhaphy and perineorrhaphy are pelvic reconstructive surgical procedures that are associated with significant postsurgical localized pain resulting from surgical incisions[10]. Similar to hemorrhoidectomy, this localized prolonged postsurgical pain seems particularly suited for the use of an extended release local anesthetic formulation. Indeed, intraoperative infiltration of a standard local anesthetic during posterior repair and perineorrhaphy has been shown to improve early analgesia and facility early postoperative recovery - decreasing pain scores and the need for rescue-opioids during the first 4 hours after surgery, limiting the time spent in postsurgical recovery phase I, and accelerating the time to first ambulation after surgery[11].These findings reiterate the need for studies investigating a slow-release, longer-acting local anesthetic formulation for patients undergoing posterior repair and perineorrhaphy. One that ideally can be integrated into an evidence-based, opioid-sparing postsurgical pain management regimen to improve perioperative care for the steadily growing pelvic reconstructive surgical patient population.

STUDY DESIGN AND METHODS

This is a randomized, placebo-controlled prospective trial offered to patients undergoing posterior colporrhaphy and/or perineorrhaphy for pelvic organ prolapse at our institution. The study will be conducted at two clinical sites:

1. Women's Center for Pelvic Health (Mercy), Carolinas Health Care System, Charlotte, NC
2. Women's Center for Pelvic Health Northeast, Carolinas Health Care System, Concord, NC

Human Subject Research and Informed Consent

Each participant will be required to sign an Institutional Review Board (IRB) approved consent form prior to beginning any study-related interventions or assessments. The informed consent form will describe the study in detail. Additionally, the study consent form will disclose the planned uses of study data, as well as potential risks to the participants. Each prospective subject will have the objectives of the study explained to them prior to enrollment. The subject will be given an opportunity to ask questions and decide whether or not to participate. Copies of the signed informed consent form will be provided to the participants, and the originals will be stored with the research records for this study at the Mercy study center.

Subjects have the right to:

- Voluntarily participate in the study

- Withdraw or refuse participation in the study at any point without questioning
- Understand the objectives of the study
- Understand the risks and benefits of the study
- Have their confidentiality maintained

Participant Screening and Point of Enrollment

Participants scheduled to undergo possible posterior repair and/or perineorrhaphy will be identified and screened against inclusion and exclusion criteria. If confirmed to meet the requirements for the study, they will be eligible to be invited to participate in the study. Participants will be consented for enrollment into the study by physicians, fellow physicians, nurse practitioners, physician's assistants, and/or a research nurse prior to surgery. Participants will be randomized to one of the two treatment groups at the completion of the surgical procedure and prior to anesthesia reversal.

Provider and Clinical Staff Training

To ensure consistent infiltration technique, the principal investigator will provide in-service education to all participating providers who will be performing surgery and incisional infiltration. Educational reviews will include medication pharmacology and specific infiltration protocol. All clinical staff, including nursing and physicians, will receive in-service training about the study protocol and guidelines.

Inclusion Criteria

1. Females age 18 and greater
2. Undergoing posterior repair and/or perineorrhaphy
    a. Concomitant surgical procedures allowed

Exclusion Criteria

1. Planned regional anesthesia
2. Allergy or contraindication to bupivacaine
    a. Severe hepatic disease
    b. Pregnant/lactating
3. Allergy or contraindication to opioids
4. Allergy to contraindication to non-steroidal medications
5. Non-English speaking
6. Inability to provide consent/decisionally impaired
7. Planned laparotomy
8. Chronic pain diagnosis
9. Chronic narcotic use (daily narcotic use for $\geq$ 3 weeks before surgery)

Study Withdrawal

Participants may withdraw from the study at any point in time. Documentation of the reason for withdrawal will be captured in the data collection forms. There will be no risk to participants that choose to withdraw from the study.

Preoperative Period

All consecutive patients planned to undergo posterior colporrhaphy and/or perineorrhaphy will be identified, screened, and approached for participation in the study. Concomitant pelvic reconstructive surgical procedures allowed. Participants who do not meet the inclusion and exclusion criteria will be considered screen failures. Screen failures will be captured and the cause for screen failure will be documented.

Perioperative and Surgery Period

All participants will receive routine preoperative intravenous antibiotic prophylaxis based on standard hospital protocols. All participants will receive standard of care induction and intraoperative analgesic medications as determined by anesthesia providers. All patients will receive prophylactic antiemetic medications perioperatively as deemed necessary by anesthesia providers. These medications will be documented in the patient's medical record and available for chart review.

Intervention: Eligible subjects will be randomized using a computer-generated randomization scheme, with patients assigned in a blinded 1:1 ratio, stratified by concurrent abdominal surgery, to either:

Group 1: 20 mL liposomal bupivacaine expanded with 10 mL of injectable sterile normal saline solution (0.9%) for a total of 30 mL.

Group 2: 30 mL of injectable sterile normal 0.9% saline solution (placebo).

The allocation sequence will be in sealed, opaque envelopes. An envelope will be retrieved in the operating room. The OR circulating nurse will assemble the appropriate intervention medication. The envelope will then be disposed of while still in the operating room in a secure manner.

Procedures will be performed by 4 fellowship trained, board-certified female pelvic reconstructive surgeons and 2 fellows in training. Subjects will be positioned in dorsal lithotomy with the use of adjustable stirrups. The patient will be prepped and draped as is standard of care at our institution, either for vaginal, or combined vaginal and abdominal surgery depending on planned concomitant surgery. After surgical timeout, a Foley urinary catheter will be placed. Concomitant procedures will be performed in the order that the surgeon deems necessary. When attention is turned to the posterior repair and perineorrhaphy, as is standard of care in our institution, the posterior compartment vaginal epithelium and perineal body will be injected with 10 mL of a local anesthetic with epinephrine for tissue dissection and hemostasis prior to incision. This local anesthetic may be diluted with normal saline to a final volume deemed appropriate by the

surgeon. All patients will receive the same amount of anesthetic in this dilution. For purposes of this study, we will standardize all patients to receive bupivacaine HCl with epinephrine prior to incision as bupivcaine HCl may be administered immediately before EXPAREL[12] without affecting the sustained release of the study drug. The vaginal epithelium is then incised as far proximal as is indicated to correct the rectocele. The vaginal epithelium is elevated and separated from the underlying connective tissue to expose the rectocele to the arcus tendineous rectovaginalis. The endopelvic fascia is then plicated with a delayed absorbable barbed suture (2-0 V-Loc), a delayed absorbable non-barbed suture (2-0 polydioxanone, PDS) or a polyglactin (Vicryl) suture in either a running or interrupted fashion. The vaginal epithelium is trimmed as is deemed necessary by the surgeon. The vaginal skin is closed with a 3-0 or 4-0 Vicryl or Monocryl suture down to the hymenal plate. The bulbocavernosus and the transversus perineal muscles are reunited in the midline with inverted sutures of PDS or Vicryl. The perineal epithelium is closed in a subcuticular fashion using 3-0 or 4-0 Vicryl or Monocryl suture. Knots are tied inside the hymeneal plane when possible to avoid pain caused by knots in the perineal body.

At the completion of the procedure and prior to anesthesia reversal, the sequentially numbered opaque sealed envelope will be opened by the circulating nurse, revealing the study group allocation**.** The surgeons will proceed with infiltration of either liposomal bupivacaine (intervention) or normal saline (control) depending on randomization. Liposomal bupivacaine has an opaque white appearance that lessons with dilution but is still visible. For this reason, surgeons injecting the study drug will not be blinded to allocation of study drug. We feel this will not significantly impact our results as patients will remain blinded and study personnel collecting outcome data will also remain blinded. Moreover, anesthesia will not observe the incision infiltration and will remain behind the patient drape. While the OR nursing and anesthesia team may see the difference in solution color, the subject and all other postoperative clinical staff (recovery nurses, floor nurses, and rounding physicians) will be blinded to study arm. Furthermore, we anticipate collection of all data by the patient's first postoperative visit, which is scheduled 1-2 weeks after surgery. Therefore, data will be collected prior to patient receiving a bill for surgery so that if the bill is itemized to include the study drug, this will not interfere with study blinding.

Intervention infiltration: Subjects randomized to liposomal bupivacaine group (Group 1) will receive a single 20-mL dose of EXPAREL 266 mg expanded in volume with 10 mL normal saline (0.9%) for a total volume of 30 mL, administered in a standardized manner in the vaginal skin and the perineal body. This technique not only approximates what is currently standard of care of infiltration of local anesthetic for this procedure but was also the technique used in prior studies evaluating the efficacy of short acting local analgesia at the time of posterior repair and perineorrhaphy[11]. Injections will be performed using a 1.5" 22-gauge needle, which is consistent with EXPAREL packaging insert use.

Active control infiltration (placebo): Subjects randomized to the control group (Group 2) will receive 30 mL of injectable preservative-free sterile normal saline (0.9%), administered in an identical fashion as described above. A placebo was used to control

for anesthesia potentially induced from tissue distention[3]. Normal saline was chosen as placebo because pre-incisional bupivacaine HCl was injected, and we feel the addition of another common anesthetic would not likely add significant anesthesia compared to the pre-incisional bupivacaine. This is a similar study design to a prior study evaluating the efficacy of liposomal bupivacaine at the time of retropubic midurethral sling placement[3].

Vaginal packing is placed at the conclusion of the procedure in the operating room at the surgeon's discretion.

Postoperative Period

Following surgery patients receive a multimodal pain regimen, standardized by an order set. This consists of ketorolac 15 or 30 mg every 4-6 hours; oxycodone with or without acetaminophen 5 mg/325 mg 1-2 pills every 4-6 hours as needed; or intravenous hydromorphone 0.5 mg or morphine 2 mg as needed if unable to tolerate oral medications. Antiemetic medications will be administered as needed including ondansetron as first line, then metoclopramide if persistent nausea. These medications will all be documented in the patient's medical record and available for chart review.

Participants will undergo a postoperative retrograde fill voiding trial per our division's standard protocol prior to discharge – on postoperative day zero for outpatient procedures or on the morning of postoperative day 1 for hospitalized participants. If vaginal packing was placed in the operating room, this is removed prior to voiding trial. The bladder is backfilled with 300 mL sterile water and patients have 90 minutes to void. Participants will pass the voiding trial if they void more than 200 mL with less than one-third post-void residual based on ultrasound assessment of residual. If they fail, a 16 French Foley catheter will be reinserted. All participants that fail the voiding trial will be discharged home with an indwelling Foley catheter. These participants will receive Foley maintenance education prior to discharge. They will be scheduled for a follow up voiding trial in the office in 1-5 days.

Depending on concomitant surgical procedures performed, patients may be discharged on the same day of surgery or on the first postoperative day. To be considered for discharge, patients must be able to ambulate independently, tolerate a diet, have adequate pain control with oral medications, and have had a voiding trial. Discharge criteria will not be altered by this study.

All patients are discharged home with prescriptions for ibuprofen 600-800 mg every 6-8 hours, oxycodone/acetaminophen 5mg/325 mg 1-2 pills every 4 hours as needed, and instructions to take Miralax, Colace, or another stool softener as needed.

Patients are advised not to place anything inside the vagina and not to lift anything more than 10 lbs until their first postoperative visit. No other activity limitations are given.

Week 2 Postoperative Visit (+/- 1 week):

Participants will be scheduled for a postoperative follow up visit, on average 1-2 weeks after surgery. They will be instructed to return their Patient Assessment Form including their pain medication diary, bowel movement diary, and VAS/NRS recordings at that visit. Finally, they will complete a patient satisfaction questionnaire at this visit.

Randomization:

A Carolinas HealthCare System biostatistician will generate a randomization sequence using SAS Enterprise Guide 6.1 (SAS Institute Inc., Cary, NC, USA). A permuted block randomization scheme will be used to assign patients in a 1:1 ratio to intervention or control. Randomization will be stratified by presence or absence of concurrent abdominal surgery. We feel this stratification of randomization sequence is necessary because we anticipate patients who undergo vaginal surgery alone versus vaginal and concurrent abdominal surgery experience a different quality and severity of postsurgical pain.

The study will be blinded such that both study participants and investigators collecting postsurgical outcome data will be masked to treatment allocation and block size randomization. The surgeon injecting the study drug will be unblinded. The pharmacist and statistician will also not be blinded, and will have no contact with the patients.

The commercial pharmacy will provide study medications - consisting of syringes containing either a 20-mL dose of EXPAREL 266 mg expanded in volume with 10 mL normal saline for a total volume of 30 mL or 30 mL of injectable normal saline solution (0.9%).

The study medications will be released by the pharmacy to the operating room nurse. At the completion of the procedure and prior to anesthesia reversal, the sequentially numbered opaque sealed envelope will be opened by the circulating nurse, revealing the study group allocation.

DATA COLLECTION AND MANAGEMENT:

Case report forms will be developed by the investigators. Data will be collected prospectively per the schedule in Table 1. All study data will be recorded by research staff and securely maintained at the Mercy study site. The data flow will consist of paper data collection for eligibility assessment, baseline data, randomization, intervention group, primary and secondary outcomes, adverse events, and protocol deviations.

Data will be entered by study staff into REDCap database that will be stored on a secure server at Carolinas HealthCare System. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. [cite: Harris PA, Thielke R, Payne J, Gonzalez N, Conde JG.

Research electronic data capture (REDCap) – a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009 Apr;42(2):377-81.] Data will be entered into REDCap within 30 business days of collection.

Each patient will have a unique identification number to which only the principal and sub-investigators will have access. The data collection spreadsheet will not contain any patient identifiers and will be password protected. The master list that links the patients and their study identification number will be stored separately from the database. All collected information will be stored separately on a password protected hard drive. A back up copy of the file will be stored on a password protected hospital network drive. All hard copies of study data will be stored in a locked cabinet in the office of the research nurse, which will also be locked.

Table 1. Data Collection Schedule

	Prior to Surgery	Surgery (Intraop)	PACU (Immediately post-op)	In Hospital Postoperative Period	Postoperative Period After Discharge (≤72 hours)	2 Week Follow up	30 day (Study Conclusion)
Informed Consent	X						
Medical History	X						
Medication review	X						
Other Demographics*	X						
Surgery**		X					
Randomization		X					
Pain scales (VAS, NRS)	X		X	X	X		
Total Inpatient Opioids (MME)		X	X	X			
Pain medication diary					X		
First opioid use (date, time)			X	X	X		
First BM			X	X	X		
Antiemetic use			X	X			
Failed voiding trial			X	X	X	X	
Adverse Events Screen						X	X
Patient satisfaction (Likert)						X	
Total Hospital Costs							X

*Other demographic data includes: Age, Race, Body Mass Index (BMI), American Society of Anesthesiologists (ASA) Physical Status classification score, Stage of posterior compartment prolapse (per pre-operative POP-Q exam), smoking status (packs per day), if sexually active (yes or no)

**Surgery data includes: concurrent surgeries performed, type of suture used in posterior repair/perineorrhaphy, site specific versus midline repair, intraoperative morphine

equivalents received, if packing placed (yes/no), surgical duration (minutes), estimated blood loss

Source of records to be reviewed:

- Canopy EMR (electronic medical record)
- Research nurse coordinator will identify charts to be reviewed based on addition of subject's name and medical record number to a general data sheet
- Patients will be discharged home with a Patient Assessment Form including a pain medication diary to complete for the first 3 postoperative days, a place to record bowel movements if this occurs during the first 3 postoperative days, and visual analog (VAS) and numerical rating scales (NRS) to record their pain intensity the evening of hospital discharge, as well as every morning and evening for the first three postoperative days.

Confidentiality of data

Electronic data will be stored to safe-guard confidentiality using a password protected computer. Principal investigator, Co-investigator, Research Coordinator nurse, and statisticians will have access to harvested patient data. Harvested patient data will be stored until final statistical analysis completed and manuscript accepted and published.

OUTCOME MEASURES

Primary Outcome Measure

The primary outcome will be assessed using visual analog scales (VAS) as well as numerical rating scales (NRS) to describe the patient's postsurgical pain intensity. The VAS is a validated 100 mm scale with "no pain" on the left equating to 0 mm and "worst pain" on the right equating to 100 mm. Subjects are asked to draw a vertical line on the scale that corresponds to their level of pain. The NRS is an 11-point scale with zero being "no pain" and ten being "worst pain". The VAS and NRS scores will be collected by blinded study personnel at multiple time points. The initial scores will be collected prior to patient transfer from post anesthesia care unit (PACU), then on the evening of postoperative day 0, and in the mornings and evenings of postoperative days 1, 2 and 3 – regardless of if the patient is in the hospital or at home. If the patient is in the hospital during these time points, their answers will be recorded by blinded study personnel. If the patient has been discharged, they will fill out their scores in the Patient Assessment Form that will be given to them prior to hospital discharge. A blinded research nurse or one of the study investigators will contact patients on the second postoperative day to remind patients to complete the Patient Assessment Form. We will also contact them prior to their postoperative appointment to remind them to return this to clinic. The Patient Assessment Form will be explained to them at the time of study inclusion and again prior to hospital discharge. See Figure 2.

Secondary Outcome Measures

Patient satisfaction with pain control: This will be assessed using a Likert Scale. The Likert scale is a 5-point scale allowing patients to rate their overall level of satisfaction with pain control as "very unsatisfied", "unsatisfied", "neutral", "satisfied", and "very satisfied". It will be collected at the patient's 2-week postoperative visit. If necessary, this can also be collected over the phone 2 weeks after surgery. See Figure 5.

Time to first opioid administration: This will be abstracted from the electronic medical record and recorded in minutes from the time patient arrives in the post anesthesia care unit (PACU) as measured by first vitals in PACU to the time of first opioid administration as recorded in the patient MAR.

Total inpatient opioid administration: This will be abstracted from the electronic medical record and recorded in morphine milligram equivalents based on the MAR. This calculation will include intraoperative morphine milligram equivalents, as well as all morphine equivalents received in the post anesthesia care unit and inpatient floor prior to hospital discharge.

Medication diary: Patients will be given a medication diary to complete at home as part of their Patient Assessment Form described above. Patients will be asked to record the date and time of all pain medications taken. We will record total milligram morphine equivalents and milligram of NSAIDs consumed at home during each of the first 3 postoperative days. See Figure 3.

Antiemetic requirements: This will be abstracted from the electronic medical record and recorded in total number of doses received as an inpatient.

Hospital length of stay: The time from admission to discharge will be abstracted from the electronic medical record and recorded in hours.

Time in PACU: This will be abstracted from the electronic medical record and recorded in minutes. Admission to PACU will be the time of first vital signs in PACU. Discharge from PACU will be time of transfer to inpatient floor or discharge home.

First bowel movement: We will record the postoperative day during which the participant has her first bowel movement – as POD#0, 1, 2 or 3. The first bowel movement will be patient-reported. If the first bowel movement occurs during the patient's hospitalization, this will be recorded by blinded study personnel. Patients will record if bowel movements occur at home during the first 3 postoperative days after hospital discharge. It is possible that patients will not yet have a bowel movement during this study time period. See figure 4.

Failed Voiding Trial: This will be abstracted from the medical record (voiding trial passed – yes or no). We will also record the date of passed voiding trial to determine how many days postoperatively this occurs (up until the 1-2 week postoperative visit). If the patient

is still not spontaneously voiding at the time of the 1-2 week postoperative visit we will record this as a voiding trial failure.

Adverse events: Any adverse event related to drug administration will be reported. Adverse events not related to medication administration will not be collected. We will however collect information on if patients are re-admitted during the study time period (yes or no). Please refer to section on Adverse Events for details of reportable criteria.

Hospital Costs: We will record total direct and indirect hospital costs, including pharmacy costs for each patient in this study. This data will come from Population Health department.

STATISTACAL CONSIDERATIONS

Statistical Methods

The data will be analyzed as intent to treat. Descriptive statistics for all variables will be calculated by study group (intervention v. control). The primary analysis will compare VAS at different hours postoperatively between study groups using Student's t test if normally distributed or the Wilcoxon rank sum test if not normally distributed. Secondary outcomes, demographics and other baseline variables will be compared between the two groups using the X^2 test or Fisher's exact test for categorical data, Student's t test for normally distributed data, and the Wilcoxon rank sum test for ordinal data or continuous data that are not normally distributed. Sensitivity analyses will be performed to assess how participants who withdrew affect the results. SAS® Enterprise Guide 6.1 (SAS Institute, Cary, NC, USA) will be used for all analyses. A two-tailed p-value of less than 0.05 will be considered statistically significant.

Sample Size Calculation

Based on prior studies and review of pain literature, a 20-30 mm difference on a continuous 100 mm VAS scale is considered clinically significant[13,14,15]. To detect a 20mm difference on VAS scores between groups, assuming a power of 80% with a standard deviation of 28 mm and an alpha of 0.05 for a two-tailed t test, it is determined that 32 subjects will be needed in each group for a total of 64 subjects. SAS® Enterprise Guide 6.1 (SAS Institute Inc., Cary, NC, USA) was used to calculate sample size.

Missing data may occur if subjects fail to return for follow-up. However, since study participants are undergoing surgery, they are more likely to return for their follow-up visits since these are a part of their standardized postoperative care. Therefore, this will decrease the rate of dropouts. To account for a 10% drop-out rate, we will aim to enroll 72 subjects with 36 in each group.

STUDY DOCUMENTATION AND MONITORING

Site Documentation

All study documents included in this protocol that will be presented to subjects will be submitted to the IRB for review. The Mercy site will maintain a study binder for all sites that will include the following:

- Enrollment log of patients that have consented to be in the study (electronic version)
- Protocol deviation log (electronic version)
- Adverse event log (electronic version)
- Investigator protocol and amendments
- IRB submissions, modifications, and renewals
- Data safety monitoring committee reports
- IRB approved consent form
- Data collection forms
- Patient assessment forms

Data Safety Monitoring

The research coordinator will complete bimonthly reports detailing the study progress and subject status, any adverse events, and any protocol deviation. The research coordinator will inform all study staff members of any unanticipated problems involving risks to study subjects or others. The research coordinator will facilitate and participate in internal monitoring visits by staff of the Office of Clinical and Translational Research at Carolinas HealthCare System. This will include a thorough review of research participant records, source documents, regulatory binders, and consent forms.

The Principal Investigator will monitor the study and assess the need for amendments as the study progresses. The PI will review the progress of each subject on the study and will apprise the IRB of adverse events or unexpected problems that may influence the IRB's decision to allow the trial to continue, in accordance with the IRB's standard operating procedures and policies. A protocol revision may be necessary for reasons including but not limited to rights, safety of participants, welfare of participants, and thus, an amendment will be required. Appropriate approvals (i.e., IRB) of the revised protocol must be obtained prior to implementation at each site.

The biostatistical team will generate periodic reports to monitor screening, enrollment, completeness of data for intervention implementation and outcomes, adverse events, and protocol deviations.

Data safety monitors will serve as an independent body to review the study data on a regular basis. The data safety monitors will include an external physician and an external research nurse. Data and safety monitoring responsibilities will consist of review of the research protocol and ongoing study activities, including review of data quality and completeness, review of fidelity to the study protocol, review of adequacy of participant

recruitment and retention, review of adverse events, and making recommendations to the study PI and to the IRB concerning trial continuation, modification, or conclusion. Such monitoring helps to safeguard subject safety, ensure data quality, and provide ongoing training and support to ensure compliance. The data safety monitors will first convene to approve the study protocol and determine the frequency of meetings. After the first ten patients are enrolled and randomized, the study statisticians will generate a report for the data safety monitors to review. Content and frequency of the reports will be agreed upon prior to implementation of the trial. The PI (Sarah Evans, MD) will be responsible for ensuring that the study complies with the data safety monitors' requests.

Study Drug Information

Medical Risks related to injection of local anesthetic, include but are not limited to, pain, bleeding, hematoma formation, infection, and/or lack of pain relief. In clinical trials, the most common adverse reactions (incidence ≥10%) following EXPAREL administration were nausea, constipation, and vomiting. Although these are common symptoms experienced by patients in the post-operative period, we will monitor for excessive reporting of these symptoms. Non-bupivacaine-based local anesthetics, including lidocaine, may cause an immediate release of bupivacaine from EXPAREL if administered together locally. The administration of EXPAREL may follow the administration of lidocaine after a delay of 20 minutes or more. Formulations of bupivacaine other than EXPAREL should not be administered within 96 hours following administration of EXPAREL. This is not applicable to our study, as we will be using bupivacaine HCl prior to EXPAREL and will not be using non-bupivacaine-based local anesthetics. Although adverse effects with the use of EXPAREL are rare, more serious adverse reactions have been reported with the use of bupivacaine-containing products. There have been reports of adverse neurologic reactions with the use of local anesthetics. These include persistent anesthesia and paresthesias. CNS reactions are characterized by excitation and/or depression. Toxic blood concentrations depress cardiac conductivity and excitability which may lead to dysrhythmias sometimes leading to death. Allergic-type reactions (e.g., anaphylaxis and angioedema) are rare and may occur as a result of hypersensitivity to the local anesthetic or to other formulation ingredients. The doses of medications in this study will be standardized and toxic doses of anesthetic therefore will be avoided to prevent the serious adverse reactions listed above.

Medical Benefits related to injection of local anesthetic: Improved postoperative pain control, reduced narcotic pain medication use and its related side effects, improved postoperative ambulation, possible shorter hospital stay, greater patient satisfaction.

Protocol Deviations

Protocol deviations will be documented and logged on the Protocol Deviations log (electronic version). This will be done for every protocol related deviation related to any portion of the study timeline. Deviations will be reviewed and evaluated on an ongoing basis, and, as necessary, appropriate corrective and preventive actions (including notification, re-training, or discontinuation) will be put in place.

Data Safety Monitoring

Data safety monitors will include an external physician and research nurse. They will be tasked to review all adverse events that occur. A semi-annual report of all adverse events will be generated and sent to the data safety monitors every 6 months.

All Serious Adverse Events (SAEs) will be reported to the data safety monitors via email within 2 business days of site staff being informed of its occurrence. The PI and research nurse will be copied on all communications with the data safety monitors. Copies of de-identified source documentation regarding the SAE will be included, as well as other clinically meaningful documentation.

The PI (Evans) will be responsible for ensuring that the study complies with the data safety monitors' requests.

Reporting Adverse Events

Adverse events (AE) will be recorded and reported per the criteria and timeline below.

All AEs must be recorded and entered into the AE log and REDCap. An event number will be assigned by each site and recorded. The DSMB will be tasked to review all adverse events that occur. A semi-annual report of all adverse events will be generated and sent to the DSMB every 6 months.

All Serious Adverse Events (SAEs) will be reported to the DSMB via email within 2 business days of site staff being informed of its occurrence. The PI and research nurse will be copied on all communications with the DSMB. Copies of de-identified source documentation regarding the SAE will be included, as well as other clinically meaningful documentation.

Reportable AEs include those determined to be related to the study medication. AEs not related to the study medications will not be collected. Please note that underlying diseases are not reportable AEs unless there is an increase in severity or frequency during the course of the investigation. Death should not be recorded as an AE, but as an outcome of a specific SAE.

Any participant that suffers an allergic reaction to the study medications will be unblinded. This will be a reported adverse event that will also be reported to the DSMB, as outlined above.

Adverse Event Definitions

Adverse Event: any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including abnormal laboratory finding) in subjects, whether or not related to study medications

Serious Adverse Event: an adverse event that led to:

- Death
- Serious deterioration in the health of the subject that either resulted in
  - A life-threatening illness or injury
  - A permanent impairment of a body structure or a body function
  - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or body function

Unrelated: No evidence that the timing of the AE has a relationship to the time study medications were taken

Possibly Related: The AE has a timely relationship to the study medications, however a potential alternative etiology may be responsible for the AE

Probably Related: The AE has a timely relationship to the study medications and the causative relationship can clearly be established. No potential alternative etiology is apparent.

Severity Definitions

Mild: Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.

Moderate: Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning.

Severe: Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.

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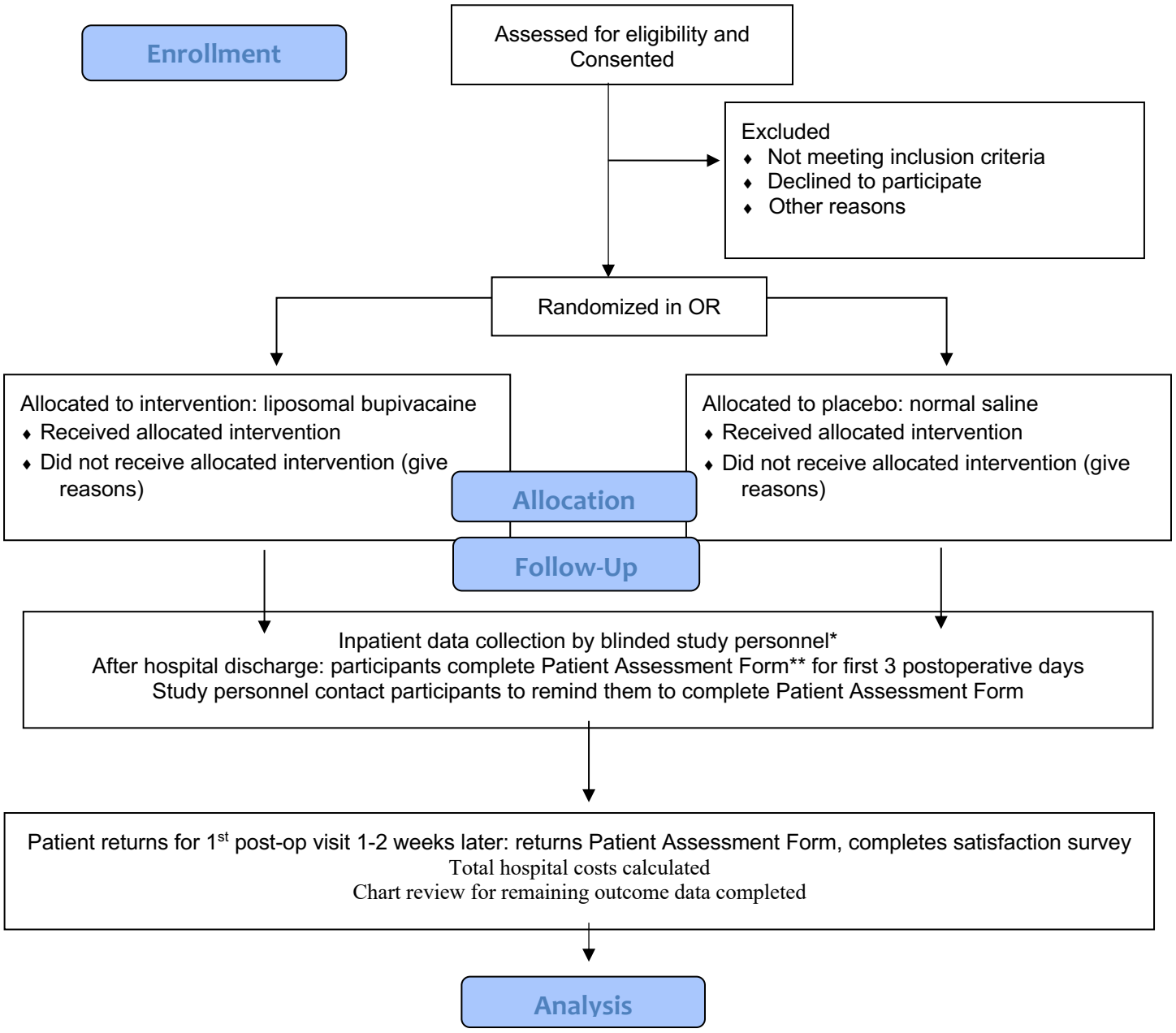
FIGURE 1. Study Trial Flow[16]



*Inpatient data collection by study personnel:

- Visual analog scales (VAS) and Numerical rating scales (NRS) prior to patient discharge from PACU
- VAS and NRS on evening of POD#0 and mornings and evenings of POD#1-3 if patient still admitted to hospital
- Date and time of first bowel movement if this occurs while patient in the hospital
- Date and time of first unassisted ambulation prior to hospital discharge

**Patient Assessment Form:

- VAS and NRS for evening of POD#0, mornings and evenings of POD#1-3 (7 total) → Figure 2
- Pain medication diary for POD#0-3 → Figure 3
- Bowel movement diary for POD#0-3 → Figure 4

Figure 2. Visual Analog Scale (VAS) and Numerical Rating Scale (NRS) with example[3]

QUESTION 1:

Please make a vertical mark on the line below that corresponds to your level of vaginal pain or discomfort now:

QUESTION 2:

Please circle the number that corresponds to your level of vaginal pain or discomfort now:

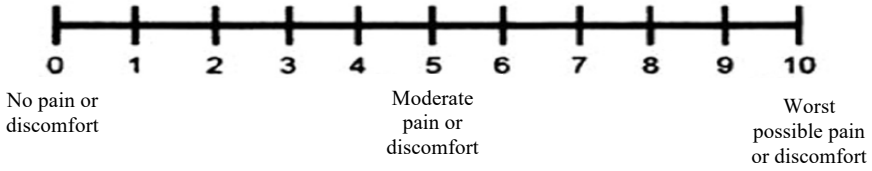


Figure 3. Medication Diary: Write down when you take **pain medications** and/or **stool softeners** today. The first line is an example. .

Time	Medication	# of pills/tablets
9 AM	Motrin	1

Figure 4. Bowel Movement Diary – *will be printed below pain medication diary for each postoperative day*

Did you have a bowel movement today? (circle one): yes no

Figure 5. Likert Scale for patient satisfaction with postoperative analgesia

Overall, how satisfied were you with your pain control after surgery?

1☐ Very unsatisfied
2☐ Unsatisfied
3☐ Neutral
4☐ Satisfied
5☐ Very satisfied

How satisfied were you with your overall surgical experience?

1☐ Very unsatisfied
2☐ Unsatisfied
3☐ Neutral
4☐ Satisfied
5☐ Very satisfied

How would you rate this surgical experience compared to prior surgical experiences?

[1] ☐ Very unsatisfied
[2] ☐ Unsatisfied
[3] ☐ Neutral, N/A
[4] ☐ Satisfied
[5] ☐ Very satisfied

Figure 6. Additional Data to be Collected by Chart Review

- Age
- Race
- Body Mass Index
- Smoking status – yes, no
- American Society of Anesthesiology (ASA) score
- Sexually active – yes, no
- Past medical history of anxiety or depression – yes, no
- Past surgical history of prior pelvic reconstructive surgical procedures – yes, no
- Mean number of medications preoperatively
- Chronic narcotic use (daily narcotic use for >3 weeks prior to surgery) – yes, no
- Stage of posterior pelvic organ prolapse on preoperative POP-Q (1, 2 or 3)
- Procedure duration, minutes
- Concurrent procedures performed
- Site specific repair (if no then presume midline) – yes, no
- Type of suture used
- Packing placed – yes, no
- Hospital admission time
- Hospital discharge time
- PACU admission time (time of first PACU vitals)
- PACU transfer time (either to home or inpatient floor)
- Total opioid consumption in milligram morphine equivalents
    - Intraoperative
    - PACU
    - Inpatient floor
- Date and time of first opioid administration postoperatively
- Number of doses of anti-emetics given postoperatively
- Discharges home with Foley catheter (i.e. failed voiding trial)
- Date and time of successful voiding trial
- Total direct and indirect hospital costs
- Total pharmacy costs
- Adverse events