

**A PROSPECTIVE TRIAL TO ASSESS ANALGESIC EFFICACY OF LIPOSOMAL
BUPIVACAINE VS BUPIVACAINE HCL AS A TAP BLOCK AFTER ABDOMINALLY
BASED AUTOLOGOUS BREAST RECONSTRUCTION**

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SCHEMATIC DESIGN

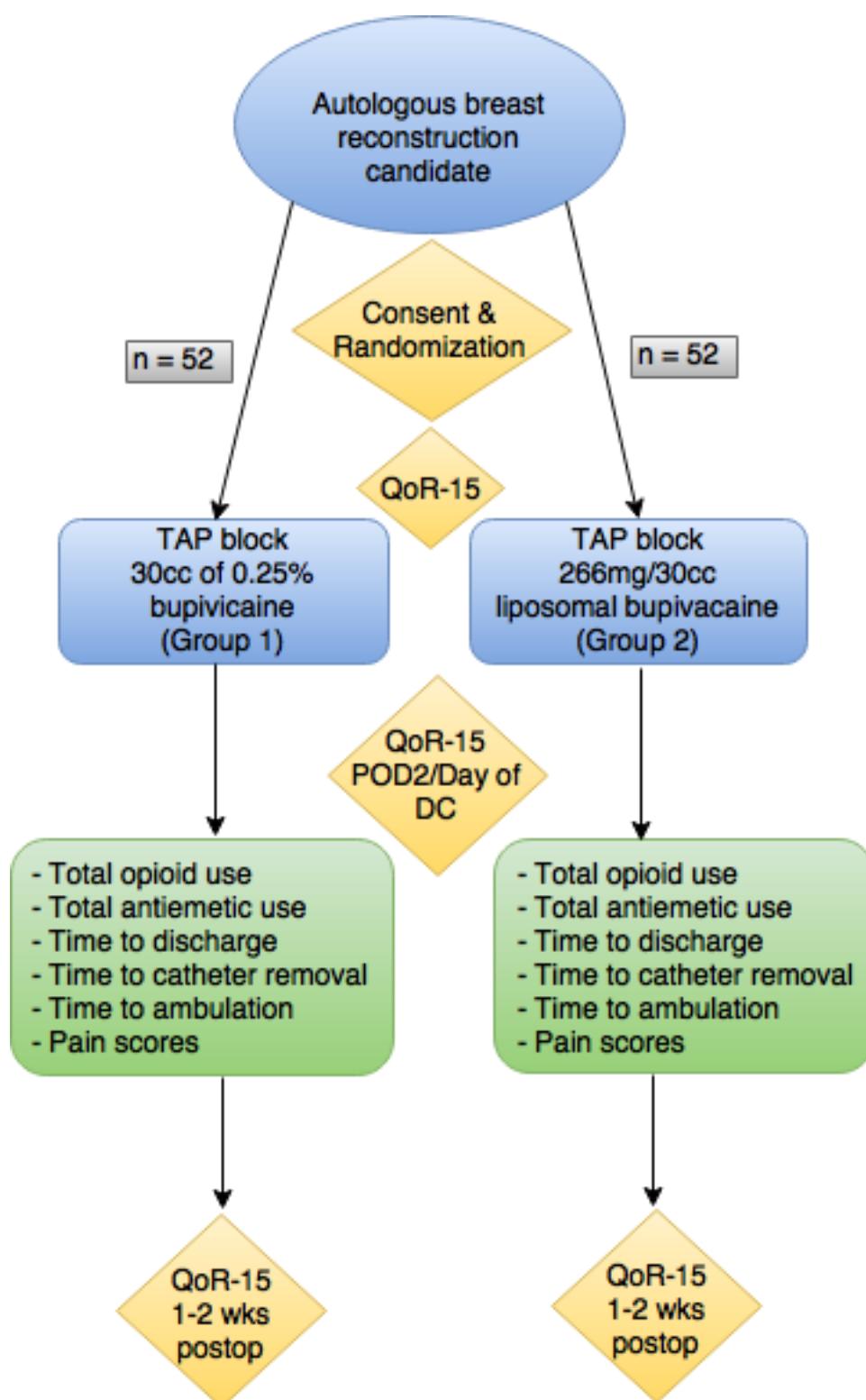


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1. BACKGROUND AND RATIONALE

1.1. Background

Abdominally-based tissue transfer for breast reconstruction after mastectomy was introduced in the early 1980s and is the primary donor site for autologous breast reconstruction^{1,2}. There were over 8,000 cases of autologous breast reconstruction performed at Barnes Jewish Hospital between 2005 and 2012³. Both the mastectomy and laparotomy sites are sources of postoperative pain; however, groups have found that the abdomen is the main source of this discomfort^{4,5}. Relieving this pain is a persistent challenge to both surgeons and anesthesiologists. The potential benefits of optimal postoperative pain control include improved cardiac, respiratory, and gastrointestinal functions, as well as fewer thromboembolic complications, fewer septic complications, and lower incidence of the development of chronic pain states^{6,7}. Opioids have been the primary form of pain control in the postoperative period, but they have been associated with nausea, vomiting, central nervous system and respiratory depression, constipation, urinary retention, itching, and the development of hyperalgesia. These consequences can significantly lengthen a patient's hospital stay and decrease their satisfaction with their procedure^{8,9}.

Several studies have shown decreased postoperative opioid use and a shorter hospital stay with the use of bupivacaine HCl in the donor site after abdominally-based autologous breast reconstruction using a transverse rectus abdominis (TRAM) and deep inferior epigastric perforator (DIEP) flap¹⁰⁻¹³. Most of these studies have also found improved patient satisfaction. However, they have either looked at a single dose of bupivacaine injected into the transverse abdominis tissue plane (TAP) (which provides only 6-8 hours of pain relief postoperatively) or the use of an indwelling catheter, which places further burden on the patient in the recovery period and requires multiple further bupivacaine instillations by the healthcare team at set time points. Current standard of care for the PI of this study is for patients to receive bupivacaine as a TAP block at the conclusion of the case. Standard post-operative medications may be found in Appendix 2 to this protocol.

Liposomal bupivacaine (Exparel) was approved for use by the FDA in 2011, and provides up to 72 hours of analgesia after surgery due to encapsulation of the drug into multivesicular liposomes allowing for controlled diffusion^{14,15}. Dasta *et al* reviewed 9 studies in which Exparel was used in orthopedic or plastic surgery settings and concluded that there was a statistically significant lower cumulative pain score at 72 hours, delayed and decreased consumption of opioids, and fewer opioid-related complications when compared to patients receiving bupivacaine HCl¹⁶. Additionally, patients undergoing abdominal surgeries such as hysterectomy and colon resection have been shown to have a lower opioid requirement and faster recovery when given a TAP block with liposomal bupivacaine when compared with those patients who have not^{17,18}.

1.1.1. Quality of Recovery – 15

The Quality of Recovery – 15 (QOR15) score was generated as a short questionnaire used to evaluate the recovery process from a patient perspective on a scale of 0-150. The questionnaire originated as a 40-question survey (QOR40), which is a global recovery survey, but was condensed and validated against both this longer version and the VAS

pain scoring system. It may be completed in less than 3 minutes, which increases the feasibility of using it in the postoperative setting.

1.2. Rationale

This study will evaluate the efficacy of analgesia provided by Exparel when compared to bupivacaine HCl as a TAP block in terms of discharge milestones, opioid use, costs, and patient-reported satisfaction at 12, 24, and 72 hours. We propose that Exparel will lower opioid use, length of stay, and overall cost of abdominally-based autologous breast reconstruction, and will lead to greater patient satisfaction.

2. OBJECTIVES

2.1. Primary Objective

To evaluate the analgesic effectiveness of liposomal bupivacaine (Exparel) versus bupivacaine HCl as a TAP block in women who have received abdominal-based autologous breast reconstruction measured by total opioid use during the hospital stay.

2.2. Secondary Objective

To evaluate the analgesic effectiveness of liposomal bupivacaine (Exparel) as a TAP block versus bupivacaine HCl as a TAP block in women who have received abdominal-based autologous breast reconstruction as measured by:

1. total antiemetic use during the hospital stay
2. length of hospital stay
3. time until ambulation
4. time until urinary catheter removal
5. pain scores
6. patient satisfaction with recovery

To evaluate the cost of liposomal bupivacaine (Exparel) versus bupivacaine HCl when accounting for length of hospital stay and use of other analgesics.

3. PATIENT SELECTION

3.1. Inclusion Criteria

1. Scheduled for abdominal-based autologous breast reconstruction (DIEP, MS-TRAM, or TRAM).
2. At least 18 years of age.
3. Female.
4. Able to understand and willing to sign a written informed consent document.

3.2. Exclusion Criteria

1. Cognitive impairment.
2. History of abdominal surgery precluding free flap donor site.
3. Allergy or intolerance to bupivacaine or “amide” anesthetics.
4. Significant preoperative chronic pain (requiring daily narcotics) or neuropathic pain (requiring daily use of pregabalin or gabapentin) within the previous 3 months.
5. Pregnant or breastfeeding.

3.3. Inclusion of Women and Minorities

Only women will be enrolled due to the anatomical specificity of breast cancer. Members of all races and ethnic groups are eligible for this trial.

3.4 Retrospective Controls

All patients who received an abdominal-based autologous breast reconstruction after 4/1/2010 but before study enrollment begins will be reviewed to evaluate the impact of other recent changes in perioperative care on the secondary objective outcome measures. Prior to this study's conception standard of care practice changed to include additional perioperative pain medications. Diet and mobility orders were also changed to adopt enhanced recovery after surgery (ERAS) standards. Quantification of the effect of these changes will add context to the effects of the liposomal bupivacaine.

The data points for this retrospective medical record review will include:

- Weight
- ASA Class (Anesthesia record)
- Anesthesia Case Duration (In OR to Exit OR time)
- Height
- 2 hour Pain Scores (PACU)
- Takeback reason if return to OR
- Postoperative Emesis
- Smoking history (CPAP assessment)
- Preoperative opioid usage
- PONV history (CPAP assessment)
- Medical comorbidities (DM, vascular disease, heart disease/CAD, CHF, respiratory disease, kidney disease, stroke, use CPAP or surgeon H and P)
- Chemo (pre surgery)
- Radiation (pre surgery)
- Breast CA Stage
- Breast CA Side
- Pectoralis muscle repair? (yes/no/unknown)
- Flap loss right? (yes/no/NA If there was no flap its NA)
- Flap loss left? (yes/no/NA)
- TTON (Time to oral only narcotics from end surgery time)

4. REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center OnCore database
3. Assignment of unique patient number (UPN)

4.1. Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below:

1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2. Patient Registration in the Siteman Cancer Center OnCore Database

All patients must be registered through the Siteman Cancer Center OnCore database.

4.3. Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

4.4. Randomization

All consenting and eligible patients (those in the prospective cohort) will be randomized at the time of their operation to receive either 0.25% bupivacaine HCl with epinephrine or Exparel as a TAP block in a 1:1 ratio. Patients will be blinded to their assignment. The randomization table will be uploaded to REDCap, and randomization will occur via an online form with entry of the patient ID number and confirmation of eligibility status. Once all information is entered, randomization is carried out via a submit button through REDCap. The randomization scheme will be generated using the SAS program PROC PLAN.

5. PATIENT VISITS

5.1. Preoperative Evaluation

The plastic surgeon will discuss treatment options given each patient's expected or acquired deformity. This decision will be based on medical/surgical history, age, patient expectations, and anatomy. If a patient is deemed a candidate for autologous breast reconstruction using abdominal tissue and she meets the eligibility criteria specified in Section 3.1, she will be approached about her ability and willingness to participate in this trial.

The Quality of Life – 15 questionnaire (Appendix 1), will be given to all patients who are potential candidates for a DIEP flap as standard of care. This module was developed to evaluate recovery after surgery. Baseline values are best assessed at a preoperative visit days to weeks prior to the surgery date. The module takes approximately 2 minutes to complete.

If a patient chooses to enroll in the study, after the consent and enrollment process this questionnaire will be entered in to the prospective study database.

5.2. Surgery, Administration of Study Intervention, and Postoperative Care

On the day of surgery, patients will receive standardized preoperative care. Uniform operative techniques will be used in both treatment groups, performed by an experienced reconstructive breast surgeon. Prior to closure of the abdominal donor site, a transversus abdominis muscle plane nerve block will be performed under direct vision. To do so, a 2cm incision will be made in the Triangle of Petit, the anatomic landmark to perform this block. The transversus abdominis muscle will be visualized deep to the external and internal oblique muscle planes and 15cc of 0.25% bupivacaine HCl with epinephrine or 15cc of Exparel will be administered on each side, or in unilateral cases, the entire amount will be given to the respective hemi-abdomen. There is no preparation of the medication required by the pharmacy; it is in 266 mg vials and is drawn into a syringe by the OR staff. The fascial incisions will be closed with standard suture. The abdominal wound will then be closed in the usual fashion.

Postoperative care will follow a standardized recovery pathway. Patients will be given standard postoperative medications and will be allowed to progress through recovery (ambulation, Foley catheter removal, and diet progression) at a rate dictated by their comfort level. Milestones including activity, foley catheter removal, diet progression, and discharge time will be recorded (Appendix 3).

Pain scores (on a scale of 1 to 10) are collected clinically every 4 hours or when pain medication is administered. These scores will be documented at 12, 24, 48, and 72 hours postoperatively in the case report forms for this study. Pain scores recorded at the closest time to each of these time points within a 4 hour window on either side, otherwise the score will be left as N/A. On postoperative Day 2 the Quality of Recovery – 15 survey will be administered. This survey will again be administered prior to discharge.

5.3. Postoperative Follow-Up Visit

Patients will return to clinic for a visit with the surgeon approximately two weeks postoperatively (+7/-9 days). Timing will vary depending on discharge date, nurse visits, and recovery. Up to 6 weeks postop is accepted before the visit will be considered out of window. The Quality of Recovery – 15 survey will again be administered. A member of the study team may contact patients over the phone or by email to assess postoperative adverse events and to complete

questionnaires.

5.4. Adverse Event Monitoring

Exparel itself can cause adverse events related to Bupivacaine toxicity. These are predominantly cardiac arrhythmias. We have previously examined the pharmacokinetics of Exparel and how this interacts with an antecedent paravertebral block. We use standard dosing of Exparel and based on our experience thus far, and planning for this study with anesthesia and pharmacology preoperatively, have had no issues with our protocol. Notably, patients who have DIEP reconstruction that uses the IMA vessels as a donor, as we do, have some tachycardia in the absence of any TAP block, bupivacaine or Exparel. We have published on this ourselves “Sachanandani, N. S., Kale, S. S., Skolnick, G. B., Barbour, J. R., Myckatyn, T. M. Tachycardia in breast reconstructive microsurgery: Affirmation of the IMA tachycardia syndrome. *J Plast Reconstr Aesthet Surg* 2015”. So, we are looking for arrhythmias beyond tachycardia when evaluating these patients for an adverse event.

The TAP (transversus abdominis plane) block, regardless of which drug is used (Exparel, Bupivacaine, or other) carries with it the risk of visceral injury by injecting the drug deep to the transversalis fascia. As such, we do the injection under direct visualization since we are already operating on the abdominal wall during this procedure, and we use a blunt-tipped cannula for injection to optimize safety. We have had no issues with this either.

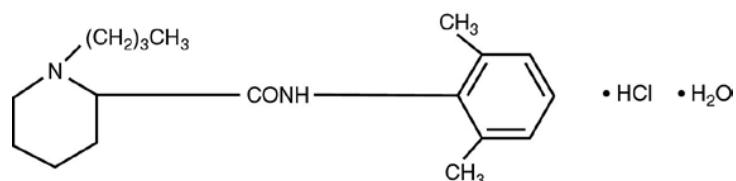
Only adverse events deemed to be serious, unexpected, severe, and related to the study drug will be recorded. Specifically, bleeding requiring blood transfusion, infection requiring readmission or surgery, life-threatening arrhythmias, wound healing problems requiring surgical intervention, and reconstructive failures due to flap loss will be recorded and evaluated for relatedness. Adverse event monitoring will begin when the study drug is administered. Adverse events that do not require clinical intervention will not be recorded.

6. PHARMACEUTICAL INFORMATION

6.1. Bupivacaine HCl

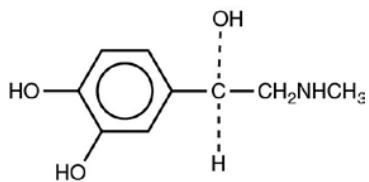
6.1.1. Bupivacaine HCl Description

Bupivacaine hydrochloride is 2-piperidinocarboxamide, 1-butyl-N-(2,6-dimethylphenyl)-, monohydrochloride, monohydrate, a white crystalline powder that is freely soluble in 95% ethanol, soluble in water, and slightly soluble in chloroform or acetone. It has the following structural formula:



Epinephrine is (-)-3,4-dihydroxy- α -[(methylamino)methyl] benzyl alcohol. It has the

following structural formula:



Bupivacaine HCl is indicated for the production of local or regional anesthesia or analgesia for surgery, dental and oral surgery procedures, diagnostic and therapeutic procedures, and for obstetrical procedures.

6.1.2. Clinical Pharmacology

Local anesthetics block the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential.

6.1.3. Pharmacokinetics and Drug Metabolism

The rate of systemic absorption of local anesthetics is dependent upon the total dose and concentration of drug administered, the route of administration, the vascularity of the administration site, and the presence or absence of epinephrine in the anesthetic solution. A dilute concentration of epinephrine (1:200,000 or 5 mcg/mL) usually reduces the rate of absorption and peak plasma concentration of bupivacaine HCl, permitting the use of moderately larger total doses and sometimes prolonging the duration of action.

The onset of action with bupivacaine HCl is rapid and anesthesia is long lasting. It has also been noted that there is a period of analgesia that persists after the return of sensation, during which time the need for strong analgesics is reduced.

PK studies on the plasma profile of bupivacaine HCl after direct IV injection suggest a three-compartment open model. The first compartment is represented by the rapid intravascular distribution of the drug. The second compartment represents the equilibration of the drug throughout the highly perfused organs such as the brain, myocardium, lungs, kidneys, and liver. The third compartment represents an equilibration of the drug with poorly perfused tissues, such as muscle and fat. The elimination of drug from tissue distribution depends largely upon the ability of binding sites in the circulation to carry it to the liver where it is metabolized.

After injection of bupivacaine HCl for caudal, epidural, or peripheral nerve block in man, peak levels of bupivacaine in the blood are reached in 30 to 45 minutes, followed by a decline to insignificant levels during the next three to six hours.

6.1.4. Supplier

Bupivacaine HCl is commercially available.

6.1.5. Storage and Stability

Store at 20 to 25°C (68 to 77°F).

6.1.6. Administration

As described in Section 5.2.

6.1.7. Special Handling Instructions

None.

6.2. Liposomal Bupivacaine (Exparel)

6.2.1. Liposomal Bupivacaine Description

Exparel is a liposome injection of bupivacaine, an amide local anesthetic, indicated for single-dose infiltration into the surgical site to produce postsurgical analgesia. Please refer to Section 6.1.1 for a description of bupivacaine HCl.

Liposomal encapsulation or incorporation in a lipid complex can substantially affect a drug's functional properties relative to those of the unencapsulated or nonlipid-associated drug. The median diameter of the liposome particles ranges from 24 to 31 μm . The liposomes are suspended in a 0.9% sodium chloride solution.

6.2.2. Clinical Pharmacology

Local anesthetics block the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential.

6.2.3. Pharmacokinetics and Drug Metabolism

Local infiltration of Exparel results in significant systemic plasma levels of bupivacaine which can persist for 96 hours. Systemic plasma levels of bupivacaine following administration of Exparel are not correlated with local efficacy.

The rate of systemic absorption of bupivacaine is dependent upon the total dose of drug administered, the route of administration, and the vascularity of the administration site.

After bupivacaine has been released from Exparel and is absorbed systemically, bupivacaine distribution and excretion is expected to be the same as for any bupivacaine HCl solution formulation.

Amide-type local anesthetics, such as bupivacaine, are metabolized primarily in the liver via conjugation with glucuronic acid.

6.2.4. Supplier

Exparel is commercially available. It will be paid for by the study.

6.2.5. Storage and Stability

Exparel vials should be stored refrigerated between 2°C and 8°C (36°F to 46°F). Exparel may be held at a controlled room temperature of 20°C to 25°C (68°F to 77°F) for up to 30 days in sealed, intact (unopened) vials. Vials should not be re-refrigerated. Exparel should not be frozen or exposed to high temperatures for an extended period.

6.2.6. Administration

As described in Section 5.2.

6.2.7. Special Handling Instructions

None.

7. REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outlined below.

The Washington University Human Research Protection Office (HRPO) requires that all events meeting the definition of unanticipated problem or serious noncompliance be reported as outlined in Section 7.2. For the purposes of this study, AEs related to the patient's surgical intervention are not reportable.

7.1. Definitions

7.1.1. Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website.

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

<http://www.hhs.gov/ohrp/policy/advevntguid.html>

For the purposes of this study, AEs related to the patient's surgical intervention are not reportable.

7.1.2. Serious Adverse Events (SAEs)

Definition: any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Any other experience which, based upon appropriate medical judgement, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

7.1.3. Unexpected Adverse Experience

Definition: any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure (or risk information, if an IB is not required or available).

7.1.4. Life-Threatening Adverse Experience

Definition: any adverse drug experience that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in more severe form, might have caused death.

7.1.5. Unanticipated Problems

Definition:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.1.6. Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subject's research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

7.1.7. Serious Noncompliance

Definition: noncompliance that materially increases risks, which result in substantial harm to subjects or others, or that materially, compromises the rights or welfare of participants.

7.1.8. Protocol Exceptions

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

IRB pre-approval of all protocol exceptions must be obtained prior to the event.

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

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any BJH or SLCH institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualified as a reportable event should be reported within 1 working day of the occurrence of the event or notification to the PI of the event.

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

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

QASMC must be notified within 10 days of receipt of IRB acknowledgment via email to a QASMC auditor.

7.4. Timeframe for Reporting Required Events

Adverse events and unanticipated events will be tracked for 30 days following the day of surgery. For the purposes of this study, AEs related to the patient's surgical intervention are not reportable. Adverse events will be graded according to the CTCAE version 4.0 form, as reflected in the CRF in the REDCap database.

8. DATA SUBMISSION SCHEDULE

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
Eligibility Checklist Medical/Surgical History Form	Prior to starting treatment
Quality of Recovery – 15	Baseline Postoperative Day 2 Prior to discharge ~2 weeks postoperatively
Hospital Stay Outcomes	At the time of discharge
Follow-Up Form	~2 weeks postoperatively
Unanticipated Event Reporting Form	At the time of any unanticipated event

9. DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least five patients have been enrolled) or one year after accrual has opened (if fewer than five patients have been enrolled at the six-month mark).

The Principal Investigator will review all patient data at least monthly and provide a semi-annual report to the Quality Assurance and Safety Monitoring (QASM) Committee. This report will include:

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

The study principal investigator and Research Patient Coordinator will monitor for unexpected events on

an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of a research related and unanticipated adverse event, it will be reported to the HRPO according to institutional guidelines.

10. STATISTICAL CONSIDERATIONS

10.1. Outcome Measures

- Primary outcome
 - Total opioid use during the hospital stay
- Secondary outcomes
 - Length of hospital stay
 - Total antiemetic use during the hospital stay
 - Pain scores (Wong-Baker scale)
 - Recovery satisfaction (Quality of Recovery – 15)
 - Length of time until urinary catheter removal
 - Length of time until ambulation
 - Cost of patient care

10.2. Study Design

All patients who are candidates for autologous breast reconstruction will be screened for eligibility for participation in this study. They will then be randomized to receive bupivacaine HCl or liposomal bupivacaine at the time of their operation. Patients will be blinded to the group to which they have been randomized. The recovery period will follow a standardized pathway to avoid heterogeneity in postoperative care and medication use.

10.3. Sample Size

A sample size of 52 in each group will be needed to achieve 80% power to detect 20.0mg difference in total opioid use at a 0.05 significance level (alpha) using a two-sided two-sample unequal-variance t-test¹⁹⁻²², assuming standard deviations of 29.0 for group 1 and 41.7 for group 2. Studies on narcotic use were from general surgery literature looking at narcotic use after TAP blocks for colectomy/ileostomy takedown, as well as use of bupivacaine after similar breast reconstruction cases in plastic surgery. This literature describes at least a 30 mg difference in narcotic use over the hospital stay between patients receiving Exparel vs. no local anesthetic after ileostomy reversal, and a 55 mg difference after open colectomy. Plastic surgery literature shows a 16 mg decrease in narcotic use over the hospital stay using implantable local anesthetic catheters after autologous breast reconstruction. The standard deviation for these studies was large at 41 mg. The 20.0 mg difference was selected based on these findings^{10,23,24}.

10.4. Data Analysis

This is a prospective single-blinded randomized control trial to evaluate the efficacy of bupivacaine HCl versus liposomal bupivacaine when given as a TAP block after autologous breast reconstruction with an abdominal donor site. For each patient, we will collect data on baseline pain and recovery variables (length of hospital stay, total opioid use, total antiemetic use, pain

score, date and time of urinary catheter removal, date and time of ambulation). Demographic and clinical characteristics will be summarized using descriptive statistics. We hypothesize that patients who receive liposomal bupivacaine will have a lower total opioid and antiemetic use, shorter hospital stay, shorter time to ambulation and urinary catheter removal, lower pain scores, and improved satisfaction. Independent t-test or Wilcoxon Rank Sum test will be used to estimate the difference in the length of hospital stay, total opioid use, total antiemetic use, pain score, date and time of urinary catheter removal, date and time of ambulation between patients given bupivacaine HCl and liposomal bupivacaine. Fisher exact or Chi-Squared tests will be applied to detect significant associations between categorical variables. All analysis will be done in SAS (Cary, USA)

11. References

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Appendix 1: QoR-15

Patient Survey (QoR-15)

Date: ___ / ___ / ___

Pre-operative

Post-operative

PART A

How have you been feeling in the last 24 hours?

(0 to 10, where: 0 = none of the time [poor] and 10 = all of the time [excellent])

1. Able to breathe easily	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
2. Been able to enjoy food	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
3. Feeling rested	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
4. Have had a good sleep	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
5. Able to look after personal toilet and hygiene unaided	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
6. Able to communicate with family or friends	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
7. Getting support from hospital doctors and nurses	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
8. Able to return to work or usual home activities	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
9. Feeling comfortable and in control	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
10. Having a feeling of general well-being	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time

PART B

Have you had any of the following in the last 24 hours?

(10 to 0, where: 10 = none of the time [excellent] and 0 = all of the time [poor])

11. Moderate pain all or nearly all of the time	None of the time	10	9	8	7	6	5	4	3	2	1	0	All of the time
12. Severe pain at any time	None or	10	9	8	7	6	5	4	3	2	1	0	All of the time
13. Nausea or vomiting	None of	10	9	8	7	6	5	4	3	2	1	0	All of the time
14. Feeling worried or anxious	None of	10	9	8	7	6	5	4	3	2	1	0	All of the time
15. Feeling sad or depressed	None of	10	9	8	7	6	5	4	3	2	1	0	All of the time

Perth, Western Australia

Abstract Total Score

Appendix 2: Standard Post-Operative Medications

Order	Dose	Route	Frequency	Start Date	Indication	Comments
Analgesics (choose all)						
<input checked="" type="checkbox"/> Celecoxib	200mg	PO	BID		Pain	
<input checked="" type="checkbox"/> Acetaminophen	1000mg	PO	Q6h		pain	
<input checked="" type="checkbox"/> Gabapentin	300mg	PO	qhs		Pain	
<input checked="" type="checkbox"/> Hydromorphone	0.5mg	IVP	Q1h prn		pain	Use while NPO. Once tolerating liquids, administer for severe pain (≥ 7)
<input checked="" type="checkbox"/> Oxycodone IR	5-10mg	PO	Q3h prn	POD#1	pain	Once tolerating liquids, use for mild to moderate pain (< 7)
<input checked="" type="checkbox"/> Oxycodone SR	10mg	PO	BID		pain	
Antiemetics						
<input checked="" type="checkbox"/> Ondansetron	4mg	IVP	Q6h prn		Nausea/vomiting	
<input type="checkbox"/> Scopolamine patch		Transdermal	Q72h		Placed preoperatively	
Constipation						
<input checked="" type="checkbox"/> Docusate Sodium	100mg	PO	BID		constipation	
Order	Dose	Route	Frequency	Start Date	Indication	Comments

Analgesic						
<input type="checkbox"/> Ibuprofen	400mg	PO	Q6h		Pain	If intolerance to celecoxib
<input type="checkbox"/> Morphine	3mg	IVP	Q1h prn		pain	If intolerance to Hydromorphone. Use while NPO. Once tolerating liquids, administer for severe pain (≥ 7)
<input type="checkbox"/> Morphine IR	7.5-15mg	PO	Q3h	POD#1		If intolerance to oxycodone. Once tolerating liquids, use for mild to moderate pain (<7)
<input type="checkbox"/> Morphine Sulfate Extended Release	15mg	PO	BID		Pain	If intolerance to oxycodone CR
Antiemetics						
<input type="checkbox"/> Prochlorperazine	10mg	PO	Q6h prn		Nausea/vomiting	

Appendix 3: Patient Milestones

Resident/nursing team: Please mark progress in charts daily. At discharge, please leave this document with the unit secretary for collection by the research team.

Patient Sticker

Post-Operative Day	
Diet	
Clear liquids	Date [REDACTED] @ am/pm
Regular	Date [REDACTED] @ am/pm
Activity	
To chair	Date [REDACTED] @ am/pm
Independent Ambulation	Date [REDACTED] @ am/pm
Other	
Foley removal	Date [REDACTED] @ am/pm
Discharge	Date [REDACTED] @ am/pm

* If patients are using > 30mg of oxycodone per day pre-operatively, call acute pain service for assistance with management