SERRATUS PLANE BLOCK FOR POST-OPERATIVE PAIN CONTROL IN BREAST SURGERY

A Randomized, Double Blind, Placebo-controlled Study at Long Island Jewish Medical Center and Center for Advanced Medicine

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LIST OF ABBREVIATIONS

AE	Adverse event
cm	Centimeter
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
ID	Identification
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
m	Meter
ME	Morphine equivalents
mg	Milligram
mL	Milliliter
MME	Morphine Milligram Equivalent
NSAID	Non-steroidal anti-inflammatory drugs
PACU	Post-anesthesia care unit
PCA	Patient-controlled analgesia
PHI	Protected health information
PI	Principal investigator

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STUDY SUMMARY

Title	*SERRATUS PLANE BLOCK FOR POST-OPERATIVE PAIN CONTROL IN OUTPATIENT BREAST SURGERY*
Short Title	*Serratus Plane Block*
Protocol Number	*15-246*
Phase	*4*
Methodology	*Double-blind, Randomized, Placebo Control Design*
Study Duration	*18 Months*
Study Center(s)	*Single-center*
Objectives	*Efficacy of Serratus Plane Block for postoperative pain management after breast surgery. Determine if use provides superior pain control to standard of care, as evidenced by decreased opioid consumption. Secondary objectives include assessments of pain, incidence and severity of opioid related adverse events including postoperative nausea and vomiting at regular time intervals, antiemetic use and overall patient experience and satisfaction.*
Number of Subjects	*90*
Diagnosis and Main Inclusion Criteria	*Breast Surgery*
Study Product, Dose, Route, Regimen	*Bupivicaine HCL, 20mL bolus of drug or placebo, 0.25% of bupivicaine.HCl or 0.9% saline, respectively will be administered underneath the fascia of the serratus muscle using ultrasound guidance.*
Duration of administration	*Single bolus before surgery*
Reference therapy	*Placebo*
Statistical Methodology	*Analysis of covariance (ANCOVA) with "type of surgery" as a covariate will be used to compare mean ME between the two groups.*

	(The inclusion of these covariates in the model is in accordance with ICH E9 Section 5.7 guidelines.)

1. INTRODUCTION AND BACKGROUND

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

Breast surgery is a common procedure performed in women. Management of postoperative pain following breast surgery is a significant challenge, but essential for reducing functional compromise and time needed for recovery. Some women who undergo breast surgery also go on to develop chronic pain syndromes. In addition to factors such as demographic characteristics and the type of surgery performed, poorly controlled, severe postoperative pain has been shown to be a risk factor for chronic postoperative pain after breast surgery (Fassoulaki et al. 2008, Iohom G et al. 2006). This chronic pain syndrome, once thought to be quite rare, is now considered a common occurrence with a prevalence of 10%-50% for patients reporting some level of chronic pain, with about 5% to 10% reporting severe or disabling pain (Kehlet et al 2006, Meretoja et al 2014).

In particular, breast surgery with general anesthesia is associated with significant postoperative pain, nausea, and vomiting, which can negatively impact patients' perioperative experience, prolonging their length of the hospital stay and result in progression to persistent pain [Vadivelu et al 2008]. In these cases, the use of opiate medication is very common and often complicated by side effects including nausea, vomiting, and constipation, and rarely complicated by more severe side effects such as decreased respiratory drive and low oxygen saturation.

Regional anesthesia, achieved through the use of nerve blocks, has been applied broadly to a variety of surgeries with excellent results in reducing the incidence of postoperative pain, opioid consumption, and related side effects such as nausea and vomiting (Hadzic 2007, Ketner et al 2011). As our knowledge of anatomy advances, new targets are being discovered for regional anesthesia. Exploring these targets enables the surgeon and anesthesiologist to provide specific anesthesia to the area being operated on while minimizing complications and systemic exposure to narcotics. Regional block techniques such as epidural [Lynch et al 1995], intercostal [Atanassoff et al 1994], interpleural [Dravid and Paul 2007] and paravertebral [Schnabel et al 2010] blocks are all acceptable techniques developed and used for breast surgery. For example, studies on thoracic parvertebral blocks for breast surgery found they provide meaningful postoperative analgesia at rest and upon arm movement in the immediate postoperative period and reduced fentanyl and postoperative analgesic requirements compared to placebo controls [Agarwal et al 2015, Faria and Gomez 2015]. However, this technique has also been associated with rapid rises in plasma concentrations of the anesthetic agents injected [Behnke et al 2002], an unreliable block

distribution for single injections [Cheema et al 1995, 2003], a reported failure rate of 6 to 12% and in rare cases pneumothorax or transient Horner's syndrome [Batra et al 2011].

The serratus plane block was developed as an alternative, safe, easily performed and effective block for providing pain relief while minimizing the liklihood of side effects assosciated with more invasive nerve block techniques nerve block techniques [Blanco, Parras et al. 2013, Blanco et al 2011]. Preliminary studies of use of this block report a prolonged numbness using a relatively small amount of local anesthetic as compared to the large volumes of local anesthetics required to provide similarly prolonged results using alternative techniques such as intercostal, interpleural and thoracic paravertebral blocks (Johnson et al 1990, Seltzer et al 1987, Karmakar et al 2005). Local anesthetics have been found to be very rapidly absorbed from the intercostal, interpleural and paravertebral spaces resulting in a potential for local anesthetic toxicity. The serratus muscle is a superficial and easily identified muscle and it has been proposed that the risk of local anesthetic toxicity after a serratus plane block is lower than most alternative regional techniques because a smaller dose of anesthetic is injected under ultrasound into a less vascularized area (Tighe 2013, Blanco et al 2013). While found to be effective in several case studies, larger studies are required to validate the introduction of the Serratus Plane Block to routine clinical practice. The potential of this technique is underlined by the six active clinical trials currently underway to assess its analgesic efficacy following thorascopic and breast surgery [https://clinicaltrials.gov/].

2. HYPOTHESIS

We hypothesize that the use of serratus plane blocks for ambulatory breast surgery postoperative analgesia will provide improved pain relief while resulting in decreased opioid usage and opioid-related adverse events such as nausea and vomiting, thus improving patient recovery and satisfaction.

3. SPECIFIC AIMS

The primary objective of this study is to determine if the use of serratus plane blocks placed before outpatient breast surgery, provide superior pain control to standard of care, as evidenced by decreased opioid consumption.

Secondary objectives include assessments of pain, anti-emetic use, incidence and severity of opioid related-adverse events including postoperative nausea and vomiting and overall patient experience and satisfaction.

4. OBJECTIVE

The authors propose a randomized, double blinded, multi-surgeon, prospective, placebo-controlled study to evaluate the effectiveness of a single shot serratus plane block in reducing postoperative pain, nausea, narcotic use, and PACU length of stay in patients undergoing ambulatory breast surgery.

5. DRUG INFORMATION

a. Product Description: Bupivacaine HCL (2.5mg/mL, AuroMedics Pharma, Dayton, NJ) is a sterile, isotonic solution containing Bupivacaine hydrochloride in water for injection in various available concentrations. Bupivacaine is related chemically and pharmacologically to the amide-type local anesthetics, including mepivacaine and lidocaine.

b. Clinical Pharmacology: Local anesthetics block the generation and the conduction of nerve impulses (1) by increasing the threshold for electrical excitation in a nerve, (2) by slowing the propagation of the nerve impulse, and (3) by reducing the rate of rise of the action potential. Systemic absorption of local anesthetics results in resolution of the local effects. 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. Local anesthetics including bupivacaine are distributed to some extent to all body tissues, with high concentrations found in highly perfused organs. Amide-type local anesthetics, such as bupivacaine, are metabolized primarily in the liver via conjugation with glucuronic acid. Elimination of the drug depends largely upon the availability of plasma protein binding sites in the circulation to carry it to the liver where it is metabolized. The kidney is the main excretory organ for most local anesthetics and their metabolites.

c. Indications and Usage: 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.

d. Dosage and Guidelines for Administration: The dose of any local anesthetic administered often varies with the anesthetic procedure, the area to be anesthetized, the vascularity of the tissues, the number of neuronal sergments to be blocked, the depth of ansethesia and degree of muscular relaxation required, the duration of anesthessia desired, individual tolerances, and the physical condition of the patient. The smallest dose and concentration required to produce the desired result should be administered. FDA information recommends 225 mg as the maximum dose. Goodman & Gilman (2004) also suggests a maximum dose of Bupivacaine 2mg/kg or 225mg, which should not be exceeded. The total dose of Bupivacaine over 24 hours should not exceed 400mg. In this study, one (unilateral) or two (bilateral) **20mL bolus of drug or placebo, 0.25% of bupivicaine HCl (in 0.9% saline) or 0.9% saline, respectively will be administered underneath the fascia of the serratus muscle for each subject using ultrasound guidance.** The total amount of bupivicaine administered will be 50mg for unilateral procedures or 100mg for bilateral procedures. An individual dose will not exceed 100mg and patients weighing less than 50kg will be excluded.

e. As there is a potential risk of severe life-threatening adverse effects associated with the administration of Bupivacaine HCl products, the serratus plane block will be administered in the

OR, where trained personnel and equipment are available to promptly treat patients who show any evidence of neurological or cardiac toxicity **as is standard of care with all local anesthetic products**. Please note the use of Bupivacaine in this study is on-label and an investigational new drug application (21 CFR Part 312) is not required. Bupivacaine HCL in this study is IND Exempt because the results will not be submitted to FDA to support a new indication or change to advertising, the planned use does not increase risks or decrease the acceptability of risks to the subjects, and the use does not require any changes to the approved formulation, dosage, or route of administration.

f. Toxicity and Known Side Effects: The incidences of adverse neurologic reactions associated with the use of local anesthetics may be related to the total amount of anesthetic administered, the particular drug used, the route of administration, and the physical status of the patient. Neurologic effects following infiltration of soft tissue may include persistent anesthesia, paresthesias, weakness, and paralysis. Central nervous system reactions are characterized by excitation and/or depression. Restlessness, anxiety, dizziness, tinnitus, blurred vision, or tremors may occur, possibly proceeding to convulsions. However, excitement may be transient or absent, with depression being the first manifestation of an adverse reaction. This may quickly be followed by drowsiness merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, and constriction of the pupils. Toxic blood concentrations depress cardiac conductivity and excitability, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest, sometimes resulting in fatalities. In addition, myocardial contractility is depressed and peripheral vasodilatation occurs, leading to decreased cardiac output and arterial blood pressure. Allergic-type reactions are very rare and may occur as a result of hypersensitivity to the local anesthetic or to other formulation ingredients. These reactions are characterized by signs such as urticaria, pruritus, erythema, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and possibly anaphylactic-like symptoms (including severe hypotension).

g. Precautions and Contraindications: Caution should be taken to avoid overdosage or accidental intravascular injection of Bupivacaine. Convulsions and cardiac arrest have occurred following accidental intravascular injection of Bupivacaine and other amide-containing products. Bupivacaine should be avoided in patients with an allergy to amide-type local anesthetics. Amide-type local anesthetics, such as bupivacaine, are metabolized by the liver and should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations and will be excluded from this study. Bupivicaine is also known to be excreted by the kidney and risk of toxic reactions to this drug may be greater in patients with impaired renal function. Patients with renal disease will be excluded from this study.

h. Drug Preparation:

Sterile plastic syringes of Bupivacaine and normal saline will be ascetically prepared (**0.25% of bupivicaine.HCl or 0.9% saline) from clinical supply upon receipt of study physician's order**. Syringes will be labeled by the unblinded study pharmacist from LIJ pharmacy with the protocol number, the subject ID (a unique randomization number generated by the Biostatistics Unit (ML, MA, also unblinded)), the date of preparation and expiration. Test articles will be checked by a second member of LIJ pharmacy to ensure that the test article assignment is appropriate.

i. Study Drug Accountability.

An accurate and current accounting of the dispensing and return of study drug for each subject will be maintained on an ongoing basis by the unblinded pharmacist. The subject number of study drug dispensed will be recorded on the Investigational Drug-Biologic Accountability Log and one of the labels will be removed and fixed to the log. The PI will verify these documents throughout the course of the study. Any returned syringes of study drug will not be used, relabeled or reassigned for use by another subject. Syringes will be discarded following use.

6. BENEFITS

This study may result in potential direct benefit to individuals that receive the bupivacaine HCL because it is believed that it will lead to the improvement of postoperative patient outcomes following surgery compared to standard of care procedures. This study may also lead to changes in future clinical care of patients undergoing breast surgery. Potential benefits of this study include expanding options for postoperative pain control, decreased need for postoperative narcotics, decreased post-operative pain, decreased need of antiemetics due to decreased nausea, and decreased PACU length of stay.

7. DISCOMFORTS AND RISKS

A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to over dosage, unintentional intravascular injection, or slow metabolic degradation. As there is a potential risk of severe life-threatening adverse effects associated with the administration of bupivacaine or any bupivacaine-containing product, this drug will be administered in a setting where trained personnel and equipment are available to promptly treat patients who show evidence of an adverse event. Although very rare, another potential risk includes an allergic reaction to local anesthetic or formulation ingredients. The most common adverse reactions to bupivacaine are nausea, constipation, and vomiting.

As a result of participation in this study (in addition to the risks associated with the surgery itself), participants are at risk for the following side effects::

a. Risks associated with bupivacaine (investigational arm only):

- Allergic reaction (including headache, dizziness, nausea, vomiting, hives and itching), nausea, constipation, vomiting, and toxicity

b. Risks associated with injection

- Pain
- Infection
- Bleeding
- Hematoma/Bruising
- Nerve injury
- Pneumothorax
- Unsuccessful block

c. Risks associated with data collection

- Breach of confidentiality.

All patients who exhibit these signs and/or symptoms will be evaluated and treated accordingly by the admitting service. This research may involve risks to patients which are currently unforeseeable. All patients will be told about any new information that might change their decisions to be in this study. Patients will be asked to sign a new consent form if this occurs.

8. SUBJECT SELECTION AND WITHDRAWAL

a. Subject Recruitment and Screening:

At pre-surgical testing, approximately one week before surgery, potential subjects will be screened and recruited into the trial.

b. Inclusion Criteria:

- Female.
- Age 18-75 years.
- ASA I-III.
- Non-pregnant.
- Undergoing outpatient breast surgery requiring general anesthesia, including but not limited to reconstruction with tissue expanders or implants and reconstruction revision.

c. Exclusion Criteria:

- Unable to provide informed consent.
- Patients who are preganant or nursing.
- ASA IV-V.
- Alcohol or narcotic dependence in the last 2 years.

- Concurrent condition requiring regular use of analgesia that may confound post-surgical assessments as determined by principle investigator.
- Hepatic disease.
- Allergies to amide anesthetics as determined from medical history or patient self-report.
- Evidence of infection at injection site.
- Contraindication to pain medications such as acetominophen, morphine, oxycodone, keterolac, dilaudid, Toradol.
- Body weight <50kg.
- BMI>50kg/m^2.
- History of hypotension.
- Abnormal renal (creatinine > 1.5 mg/dL) function.
- Heart block.
- Any physical, mental or medical condition, that in the opinion of the investigator, makes study participation inadvisable. For example, chronic pain conditions, significant medical disease, laboratory abnormalities or condition(s) that could impact a subject's ability to communicate with the study staff, complete study activities such as provide pain scores, or would otherwise contradict study participation

d. Informed Consent

Informed consent will be obtained for all surgical procedures and for participation in this study. Patients without capacity to provide informed consent will be excluded from the study. At pre-surgical testing, subjects screened will be recruited into the trial. Those wishing to participate will sign the informed consent form. Subjects who sign a consent form will be randomly assigned on the day of their surgery to have either placebo or bupivacaine serratus plane block. Subjects will be allowed to keep the consent form to review and sign on the day of surgery if they require additional time to consider participation in the study. Informed consent will be conducted as follows: During their pre-surgical testing appointment, the anesthesiologist or pre-surgical testing physician will discuss the following:

- the purpose/objective of the study;
- the study design (e.g., the number of participants);
- the details of each pain management regimen (including their risks and benefits);
- how patients are assigned to the investigational and control groups (i.e., randomly);
- the methods by which the study will monitor the patient's pain;
- risks/benefits;
- participation in this study is not required for receipt of either postoperative analgesia; regimen;
- patients may withdraw from this study at their discretion;
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9. EXPERIMENTAL DESIGN

a. Overview:

This is a randomized, double-blind, placebo-controlled trial of serratus plane block in subjects undergoing unilateral or bilateral breast surgery at Long Island Jewish Medical Center. Ninety subjects will be enrolled into the study at presurgical testing approximately one week before their surgery. Subjects will be stratified based on surgery type and randomized to receive a serratus plane block with either bupivicaine HCL or normal saline in a 1:1 ratio. All patients will receive standard intraoperative anesthesia and standard postoperative pain control.

- **Control Group:** Each patient in the control group will receive standard intra-operative general anesthesia and standard post-operative pain control as a well a placebo injection of normal saline on the operated side(s) using the same technique as the serratus plane block.
- **Investigational Group:** Each patient in the investigational group will receive serratus plane blocks on the operated side(s) using bupivicaine HCl. This will be in addition to standard of care intra-operative anesthesia and standard of care post-operative pain control. One (unilateral) or two (bilateral) 20mL bolus of drug, 0.25% of bupivicaine.HCl, will be administered underneath the fascia of the serratus muscle for each subject using ultrasound guidance. The total amount of bupivicaine administered will be 50mg or 100mg for unilateral and bilateral procedures, respectively.

b. Randomization:

The Biostatistics Unit (BU) will develop a computer-generated randomization list that utilizes a permuted block design, and will develop and implement a well-documented double-blind randomization procedure. Details of the procedure, including required record keeping, will be further developed upon approval of this protocol.

A unique randomization number will be generated by the Biostatistics Unit for each subject in the trial with the format RZxyyy. The randomization number will be a 4-digit number with the following format: the 1st digit (x) will designate the **TYPE OF SURGERY** [1=Breast reduction/mastopexy, 2=Breast augmentation, 3= Revisions & Other] and the last 3 digits (yyy) will be numbered sequentially starting with "001". For example, the third subject randomized to "Breast augmentation" will have the randomization number RZ2003.

Subjects will be randomized to either Placebo (saline) or Bupivacaine injection as described below. Randomization will be double blind. Preparation of blinded injection is described below.

c. Blinding and Injection Preparation:

Sterile, sealed, plastic syringes of clinically available supply of normal saline (0.9%) and bupivacaine.HCl (0.25%) will be prepared asceptically by the unblinded study pharmacist (Z. Faynblatt) at Long Island Jewish Medical Center Pharmacy upon receipt of study physician's orders. The study pharmacist will have access to the full randomization scheme and will prepare the sterile syringe with a 2-part tear off label. Both parts of the label will contain a randomly generated 4-digit number generated by the Biostatistics Unit. In addition to noting the number, one

of these labels will be attached to the drug accountability paperwork when the drug is dispensed. The second part of the label will remain affixed to the syringe and will be attached to data collection sheet by the study anesthesiologist administering the drug. Syringes will be prepared upon receipt of study physicians orders. Any test articles to be administered will be checked by the pharmacist and a second member of LIJ pharmacy.

d. Surgery:

All breast surgery will be performed under general anesthesia as per standard of care. The type of surgery and laterality will be recorded.

1. Opioids will be utilized at the discretion of the study anesthesiologist for intraoperative pain control.
2. Regardless of whether a subject is enrolled in the investigational arm or control arm of the study, the breast surgery will take place in the usual fashion.
3. Prior to surgery, upon receipt of physician's orders, the randomization system will be accessed by the pharmacist and the treatment and randomization/subject ID number will be obtained. The syringe will be prepared and the randomization/subject ID number will be confirmed to match the randomization system by a 2nd member of the pharmacy staff.
4. This syringe (prepared upon receipt of physician's orders) will be collected from pharmacy and brought to the OR.
5. For patients enrolled in the investigational arm of the study, prior to surgery, following induction of general anesthesia, serratus plane block (**20mL bolus of drug, 0.25% of bupivicaine HCl will be administered underneath the fascia of the serratus muscle for each subject using ultrasound guidance)** will be performed on the operated side(s) (See section "Investigational Study Group" for further details).
6. For patients enrolled in the control arm of the study, prior to surgery, a placebo injection of normal saline will be performed on the operated side(s) using the same technique as the serratus plane block with bupivicaine (**0.9% saline administered underneath the fascia of the serratus muscle for each subject using ultrasound guidance).**

e. Investigational Study Group

1. In the operating room before surgery, patients enrolled in the investigational study group will receive an injection of bupivacaine as a serratus plane block on the operated side(s) in the standard fashion.
2. After the surgery is complete, patients will be awoken from general anesthesia, extubated, and transferred to the PACU.
3. Patients will receive oral standard post-operative pain and nausea management on an as-needed basis in the PACU.

f. Control Study Group

1. For patients enrolled in the control study group, the procedure takes place in the usual fashion. Patients in this group undergo a placebo injection of normal saline on the operated side(s) at the same time, using the same technique as the serratus plane block.
2. After the procedure is complete, patients will be awoken from general anesthesia, extubated, and transferred to the PACU.
3. Patients will receive oral standard post-operative pain and nausea management on an as-needed basis in the PACU.

g. Data Collection:

In addition to basic demographic information, the patients post-operative course will be reviewed. Information to be collected:

1. Medical record number;
2. Date of surgery;
3. Type of Surgery
4. Race/Ethnicity
5. Length of PACU stay (hours);
6. Age at time of surgery (years);
7. Height (cm);
8. Weight (kg);
9. Body mass index (kg/m^2);
10. Indication for procedure;
11. Surgical procedure(s) performed;
12. Attending breast surgeon (for patients having concurrent breast surgery)
13. Attending plastic surgeon
14. Length of procedure (hours);
15. Perioperative intravenous administration (including dose) of fentanyl, Tylenol, and Toradol;
16. Postoperative intravenous administration (including total dose) of morphine, dilaudid, Tylenol, toradol, and other analgesic agents;
17. Postoperative oral administration (including total dose) of Percocet, morphine, dilaudid, Tylenol, Toradol, and other anlagesic agents;
18. Postoperative oral and IV use of antiemetics (Zofran, etc).
19. Self-reported pain score using the 0–10 Numeric Pain Rating Scale.
20. Self-reported nausea score using the 0–10 Numeric Pain Rating Scale.
21. Vomiting episodes
22. Past medical history including diabetes mellitus, history of neuropathy (of any etiology), history of seizures, pre-existing pain conditions, and regular (defined as use > 3 times weekly) analgesic use (including type of analgesic used), allergies or adverse reactions to NSAIDs or opiates;

The study will collect pain and nausea scores in the PACU every 30 minutes up to 4 hrs and at 1 hr intervals after 4 hours for the duration of PACU stay. With respect to timing of collection of scores, time zero will be PACU admission and all time intervals for pain score assessment will be determined using this time as a reference. Investigators will also follow up within one week of surgery to determine patient satisfaction and collect pain scores documented by patients following discharge.

h. Endpoints:

1. ***Amount of narcotic administered(morphine miligram equivalents).***
   The primary endpoint will be narcotic usage for the first 4 postoperative hours. Postoperatively, oral and IV rescue medication will be administered to both groups upon request as per standard of care. The use of narcotics will also be recorded intra-operatively, for the duration of PACU and hospital stay and up until the end of postoperative day one. Consumption of rescue medication will be converted to the morphine equivalent (ME) dose for analysis. Analysis will be performed on both groups to allow comparison of effect of block with placebo and bupivicaine on total opioid consumption.
2. ***Postoperative Pain.***
   Postoperatively, pain intensities at rest and on movement will be assessed every 30 minutes in the PACU for the first four hours and at hourly intervals up until PACU discharge, using the visual analog scale (VAS) with two anchor points; 0 being no pain and 10 being the worst pain imaginable. Following discharge patients will be asked to record their pain upon and one hour after taking their pain medication up until the end of the first postoperative day.
3. ***Postoperative Nausea (Incidence and rating).***
   Evaluation will be performed at every 30 minutes in the PACU for the first four hours and at hourly intervals up until PACU discharge using a standard 11-point verbal rating scale, for which "0" represents "no nausea" and 10 represents "worst nausea imaginable." Significant nausea is defined as a score of ≥ 4.
4. ***Vomiting.***
   This will be recorded throughout PACU stay until discharge. Vomiting will be measured as the number of emetic and retching (recorded separately) episodes occurring at least 1 minute apart during entire PACU stay. Severe vomiting will be defined as 3 or more episodes during a given time interval. Vomiting and retching episodes will be counted as necessary up to PACU discharge.
5. ***Amount of antiemetic administered.***
   Amount of antiemetic administered intra-operatively, during PACU and hospital stay will be recorded.
6. ***PACU Length of Stay.***
7. ***Patient Experience and Satisfaction.***

Patient satisfaction with postoperative pain and and overall patient satisfaction with their surgical experience will be assessed within one week following discharge with a follow up phone call using a 5-point categorical scale.

i. Statistical Considerations

1. ***Brief Summary:*** This is a double blind randomized, placebo controlled trial of Bupivicaine vs Placebo for the treatment of post-op pain following oupatient breast surgery.
2. ***Primary Endpoint:*** Narcotics usage (IV or PO) for first 4 hours in the PACU, expressed as morphine equivalents (ME) .
3. ***Secondary Endpoints:*** Narcotic usage for the duration of PACU and hospital stay and up to postoperative day one, antiemetic administration in PACU (no, yes); PACU length of stay, Self-reported pain using the 0–10 Numeric Pain Rating Scale during the first 4 hours of PACU stay, hospital stay and up until the end of the first postoperative day. Self-reported nausea, vomiting episodes during PACU stay and patient satisfaction with pain management.
4. ***Statistical Methods:***

   Primary - Analysis of covariance (ANCOVA) with "type of surgery" as a covariate will be used to compare mean ME between the two groups. (The inclusion of these covariates in the model is in accordance with ICH E9 Section 5.7 guidelines.) Data transformation (presumably a log transform) will be considered in order to achieve the required assumptions of normality and equal variance.

   Secondary – The chi-square test will be used to compare anti-emetic rates and patient satisfaction. ANCOVA will be used to compare LOS. pain and nausea scores.
5. ***Intention to Treat (ITT):*** The ITT population will be defined as all subjects who are randomized. All primary analyses will be carried out on the ITT population.
6. ***Sample Size Consderations:*** A two-sample t-test approach is used as a reasonable simplification of the ANCOVA method. Based on previous data, it is expected that the Placebo group will average 12 ME (SD=4) of narcotics in the PACU. A reduction of 20% to 9.6 ME in the Bipuvacaine group would be clinically significant. A sample size of n=45 subjects per group (total 90) will yield 80% power to detect such a reduction (alpha=0.05, 2-tailed t-test).
7. ***Interim Analysis:*** There will be no interim analysis for early stopping of the trial.

j. Adverse events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE therefore is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to the investigational product. An unexpected AE is one of a type not identified in nature,

severity, or frequency in the study protocol or of greater severity or frequency than expected based on the information in the study protocol.

AEs will be reported in the patient's medical record and reviewed by the PI, who records, reviews, evaluates, and manages all AEs. Any unanticipated problems which occur will be primarily addressed by the principal investigator and other physician investigators. Serious AND Unanticipated AND possibly, probably or definitely related AEs will be reported to the IRB as per their specific reporting requirements. Modifications to the protocol, if required, will be determined by the PI in cooperation with the IRB. Abnormal results of diagnostic procedures are considered to be AEs if the event:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Adverse events will be classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events will be defined as those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. All adverse events that do not meet any of the criteria for serious will be regarded as ***non-serious adverse events***.

1. Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition will be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

2. General Physical Examination Findings

At screening in pre-surgical testing, any clinically significant abnormality will be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

3. Post-study Adverse Event

All unresolved adverse events will be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. The investigator will instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator will notify the IRB of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study.

Abnormal Laboratory Values

A clinical laboratory abnormality will be documented as an adverse event if <u>any one of the following</u> conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

4. Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization will be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event. The condition, hospitalization, prolonged hospitalization, or surgery will be reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery will ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

k. <u>Recording of Adverse Events</u>

At each contact with the subject, the investigator will seek information on adverse events by continuous monitoring while subject is under anesthesia, specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results will be recorded in

the source document, though should be grouped under one diagnosis. All adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

l. Reporting of Serious Adverse Events

Reports of all serious adverse events (including follow-up information) will be submitted to the IRB according to their policies. Copies of each report and documentation of IRB notification and receipt will be kept in the research binder.

m. Unblinding Procedure

The unblinding procedure will ensure that the identity of the investigational medicinal product is only revealed as far as necessary. The subject's treatment will be revealed when it is necessary to ensure the subject's safety and/or this information would be instrumental in further treatment decisions during a medical emergency and/or a suspected unexpected serious adverse event. Pharmacy personnel with access to the randomization scheme will be contacted using a designated telephone number. If a subject's treatment is unblinded, this will be reported to the IRB as per guidelines and documented on the CRF (date and initials of investigator) with details of the time and reason for unblinding.

n. Stopping Rules

This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) any new information becomes available during the trial that necessitates stopping the trial; or (3) other situations occur that might warrant stopping the trial.

o. Medical Monitoring/ Data and Safety Monitoring Plan

In accordance with federal guidelines, this study requires a DSMP. It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

The PI has appointed an independent Safety Officer/Medical Monitor to fulfill the data and safety monitoring responsibilities. The director of Regional Anesthesia at Northwell Health and medical director of Franklin Hospital, Dr. Joseph Marino MD, will serve as the data and safety monitor along with Khang Nguyen, who will offer ancillary support to the monitoring responsibilities. Dr. Marino does not have any scientific, financial, or other conflict of interest related to the study and is not responsible for any patient care at Long Island Jewish Medical Center. Safety will be

monitored after the first 5 patients and at 6 month intervals afterwards by the study team and the Safety Officer/Medical Monitor throughout the duration of the study. The PI will prepare a safety report for these regular reviews comprised of adverse events and the actions taken. The PI will contact the Medical Monitor for ad hoc reviews of any unanticipated safety events. The study protocol will be carried out in accordance with OHRP/FDA/NIH guidelines and requirements. In the event of a serious adverse event during the study protocol, it will be reported immediately to the PI, the co-investigators, and the Medical Monitor. Serious AND Unanticipated AND possibly, probably or definitely related AEs will be reported to the IRB by the principal investigator as well as to all members of the research team. Data will also be reviewed to determine if aspects of the study need to be changed or stopped. In addition, the monitor will review any and all deviations, adverse events and unanticipated problems that may occur to determine their relatedness to the study, their severity, and whether they require study changes. In addition, any unanticipated problems will be reported to the IRB as per their specific reporting requirements. Anticipated deviations will be submitted to the IRB for approval as a protocol exception prior to its initiation, unless required to eliminate apparent immediate hazards.

The primary concern when administering local anesthetics is the development of local anesthetic toxicity or anaphylaxis. With respect to this study, the risks of local anesthetic toxicity after a serratus plane block is lower than most alternative regional techniques because a smaller dose of anesthetic is injected under ultrasound into a less vascularized area (Tighe 2013, Blanco et al 2013). With respect to anaphylasis, patients with a suspected allergy to local anesthetics based on medical history and patient self report will be excluded from the study. Subjects will also be continuously monitored in the OR during the bupivicaine injection and for the duration of surgery for these potential adverse events by: electrocardiogram, blood pressure and arterial oxygen saturation. The PI (or another designated Investigator in his absence) will be notified of any abnormal results so that standard of care safety measures outlinedare implemented. The primary physician will also be notified of any abnormal results and any changes to the subject's care, and will also be provided with the test results. The use of single-shot regional anaesthetic techniques is associated with few complications. The expected risks are as follows:

Allergic reaction, toxicity and effects associated with injection**:**

Monitoring: following first 5 subjects enrolled and at 6 month intervals.

Actions: If there is any indication of allergy to local anesthetics in patient medical records or patient reports allergy at screening, subject will not be enrolled. If there is any indication of allergic reaction during injection, injection will be discontinued immediately but patient will continue to be followed until end of study. Signs of allergy at any study visit, such as headache, dizziness, nausea, vomiting, hives and itching will be recorded as AEs. With respect to toxicity investigators will use slow, incremental injections of local anesthetic, while monitoring the patient for signs of toxicity. Early recognition of the toxicity and early discontinuation of the administration is of crucial importance. Any signs of toxicity such as hypotension, severe hypotension, reduced cardiac output, and/or malignant arrhythmias will result in the administration of local anesthetics being

stopped immediately and patient parameters will be continuously assessed until the patient is completely asymptomatic and stable and the event recorded as an AE. Events associated with injection include block failure, pain, infection, bruising/hematoma, nerve injury, and pneumothorax. Symptoms of injection related events will be treated and checked at appropriate intervals in addition to any other clinical testing requested by primary physician.

The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

p. Discontinuation of Study / Subject Withdrawal

Patients may withdraw from this study at their discretion. The study may be discontinued at any time at the discretion of the PI.

10. **DATA HANDLING AND RECORD KEEPING**

Any paper documents that contain PHI (e.g., link between the ID to subjects' identifiers) will be stored in a locked cabinet within the anesthesiology research office, separately from any de-identified research documents. IRB-approved personnel will be the only individuals with access to any research documents containing PHI.

Any electronic documents that contain PHI will be stored on REDCap. The Feinstein Institute for Medical Research will be used as a central location for data processing and management. Vanderbilt University, with collaboration from a consortium of institutional partners, has developed a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. REDCap (Research Electronic Data Capture) data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the Biostatistics Unit of the Feinstein Institute for Medical Research. The iterative development and testing process results in a well-planned data collection strategy for individual studies. REDCap servers are housed in a local data center at the Feinstein and all web-based information transmission is encrypted. REDCap was developed specifically around HIPAA-Security guidelines and is recommended to Northwell Health researchers by both our Clinical Research Service, Research Compliance Office and Institutional Review Board. REDCap has been disseminated for use locally at other institutions and currently supports 1,244 active institutional partners and other institutions in 87 countries (www.project-redcap.org).

No PHI or research data will be stored on any Portable Electronic Devices (e.g., laptops, tablets, flash drives, etc.).

Any research data that will be emailed will be de-identified and encrypted. PHI will not be emailed to any commercial email addresses (e.g., Gmail, Yahoo, Hotmail).

Data safety will be monitored on an ongoing basis by the PI and in the event that a problem occurs, the problem will be managed by the PI and reported to the IRB according to requirements

11. **DATA DISCLOSURE/PUBLICATION**

Investigators intend to publish the results of this study. Any published results will only include an aggregate of de-identified data. No protected health information will be disclosed outside of Northwell Health for the purposes of this research.

Protected health information may be shared with:

- The Institutional Review Board (IRB) at Northwell Health;
- Doctors and staff at the hospital where this research study will take place;
- Doctors and staff at other institutions that are participating in the research study;
- Data and Safety Monitor(s), independent expert(s) that review the information from this research throughout the study; and/or
- Governmental entities that have the right to see or review your protected health information, such as the U.S. Office of Human Research Protections and the FDA.

Protected health information will only be used and/or given to others to perform this research; to study the results; and to determine if the research was done correctly. All reasonable efforts will be made to maintain confidentiality (in accordance with the measures outlined above).

13. CONFLICT OF INTEREST

The investigators have no conflicts of interest to report.

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