Enhanced pain control after reduction mammaplasty with bupivacaine and dexamethasone regional block

1) Abstract of the study

Background: Patients undergoing reduction mammoplasty frequently suffer significant post procedure pain at the operative site. While regional nerve block is routinely performed with bupivacaine, the effects of this are limited to the up to 8 hours of action provided by this drug. Previous studies in orthopedic and thoracic surgery patients have demonstrated that addition of dexamethasone to the perineural block prolongs the duration of analgesia. This has never been studied in the plastic surgery patient. We propose that addition of dexamethasone to the infiltration solution will prolong the duration of analgesia provided by a regional block and reduce the need for adjunct narcotic medication in the postoperative period following reduction mammaplasty.

Methods: Patients undergoing elective Breast Surgery at Temple University Hospital will be randomized to receive a control standard perineural block with 19-mL 0.5% bupivacaine +1mL 0.9% sterile saline or block with the experimental mixture of 19mL 0.5% bupivacaine + 1mL 4mg/mL dexamethasone solution for each breast. Primary end points will be mean pain VAS score as measured every 4 hours postoperatively and postoperative narcotic consumption data during the admission following the procedure. Secondary endpoints also observed will be anti-emetic consumption, vital signs, quality of life as assessed by SF-36 and Breast-Q questionnaires, and length of hospital stay.

2) Protocol Title

Enhanced pain control after reduction mammaplasty with bupivacaine and dexamethasone regional block

3) IRB Review History

No previous submissions

4) Investigator

Andrew Gassman, MD, Gaurav Trehan MD,

5) Objectives

This study aims to evaluate the effect of the addition of dexamethasone to a standard bupivacaine nerve block following reduction mammaplasty. We propose that addition of dexamethasone to the infiltration solution will prolong the duration of analgesia provided by a regional block and reduce the need for adjunct narcotic medication in the postoperative period following reduction mammaplasty.

6) Background

Enhanced pain control after reduction mammaplasty with bupivacaine and dexamethasone regional block

Breast reduction is among the most common procedures performed by the Plastic Surgery division at Temple University Hospital. These patients are generally admitted for 23 hour observation primarily due to significant postoperative pain. Currently regional nerve block is routinely performed with bupivacaine infiltration. This provides effective immediate postoperative pain control but is limited by the 2 to 8 hour duration of action provided by this drug. These patients typically require significant amount of narcotic analgesia in the postoperative period. Exparel® (bupivacaine liposome injection) is a commercially available long acting formulation of bupivacaine however its significant cost has been deemed prohibitively high for use at this and most other institutions.

A number of studies in the anesthesia literature have demonstrated that addition of dexamethasone to bupivacaine when administered as a perineural block extends the duration of analgesia. In Bjorn, et al. (Reg Anesth Pain Med, 2016 Dec) saphenous nerve block with 10mL 0.5% bupivacaine + 1mL 0.4% dexamethasone after ankle surgery significantly extended the time to first narcotic request compared to control with bupivacaine alone. Maher, et al. (Pain Med, 2016 Jul) examine the use of both IV dexamethasone (8mg) and combination perineural dexamethasone and bupivacaine as intercostal nerve block during VATS. They demonstrate statistically significant decrease in pain at 8, 20, and 24 hours postoperatively. Other studies have obtained similar results in a variety of orthopedic and neurosurgical procedures.

A PubMed search using terms “dexamethasone” and “nerve block” did not return any studies that pertain to plastic reconstructive surgeries including but not limited to breast reduction. Additionally, searches using “breast reduction” and “nerve block” or “mammaplasty” and “nerve block” returned only 1 relevant study that examines the use of Exparel® nerve block during mastectomy (Abdelsattar 2016). Again, no studies examine methods of prolonging the duration of regional anesthesia after reduction mammaplasty

7) Setting of the Human Research

This study will be performed exclusively at Temple University Hospital. Patients will initially be identified and recruited during the preoperative clinic visit. The study will again be described to the subjects and consent obtained in the preoperative holding area prior to the procedure.

8) Resources Available to Conduct the Human Research

The Plastic Surgery division at Temple University Hospital performs an average of 10 breast reduction mammaplasty procedures per

month. We anticipate that the vast majority of these patients will be eligible for study enrollment and will agree to participate in the study due to the potential for improved pain control

Data collection is expected to occur over a period of 12 months. Much of this will be collected automatically from Epic patient data. With the assistance of the medical informatics department, an automated data collection framework is being developed.

This study will be led by Dr. Andrew Gassman of the Plastic and Reconstructive Surgery Division and Dr. Gaurav Trehan from the Department of Anesthesia. Dr. Gassman is an experienced researcher with multiple publications in the field of plastic surgery. He has a specific research interest in pain control. Dr. Trehan is a specialist in pain medicine. He completed a fellowship in pain medicine at the University of Pennsylvania. He has book chapters and publications in the field of pain medicine.

Research Support will be provided by plastic surgery and general surgery residents. Total project staff is expected to total at least 5 people. We expect this to be more than adequate to conduct this research

Enrolled subjects will be admitted patients at Temple University Hospital. They will have access to all of the medical and psychosocial services provided to patients of the hospital in the event of an adverse outcome as a result of participation in this study

All persons involved in conducting this study will be fully briefed on the background and protocol by the primary investigator or study coordinator prior to any involvement with the study. There will be ongoing oversight by the PI and study coordinator of all study subjects and personnel.

9) Prior Approvals

No prior approvals are required. The Division of Plastic and Reconstructive Surgery and the Department of Anesthesia have approved this study.

10) Study Design

a) Recruitment Methods

Research subjects will be identified in the plastic surgery clinic when they are scheduled for breast reduction surgery. The study

will be described to patients when they agree to surgery. They will again be briefed on the study on the day of surgery. No additional recruitment methods will be required. No compensation will be provided to study participants.

b) Inclusion and Exclusion Criteria

Initial in office screening will easily identify all patients who are requesting and scheduling breast reduction surgery. Criteria to be included in the study are women aged 18-80 undergoing elective bilateral breast surgery with ASA class 1-3.

Exclusion criteria are allergy to any of the study medications, history of chronic pain condition or narcotic dependency, history of chronic renal or hepatic disease, history of diabetes mellitus, and history of previous post operative nausea and vomiting. Prisoners and pregnant patients will also be excluded. Screening for appropriate subjects will occur in the clinic. ASA determination will be made by the anesthesia department during preoperative testing.

c) Local Number of Subjects

An average of 10 breast reductions are performed monthly at Temple University Hospital. We expect nearly all of these patients to meet screening criteria and to agree to participate in this study

d) Study-Wide Number of Subjects

This is a single site study. Anticipated number of subjects is approximately 60

e) Study Timelines

- Data collection will occur over a period of 12 months
- Interim analysis will be conducted by an independent at 6 months to confirm the quality of the data
- Patient participation is limited to the length of the hospitalization for breast reduction procedure plus the first postoperative visit. For most subjects this will be 24 hours as inpatients with the postoperative visit occurring 1 week after surgery.

f) Study Endpoints

Primary study endpoints are average VAS pain score during hospitalization and postoperative narcotic usage during the hospitalization. Secondary endpoints are need for antiemetic therapy, length of hospitalization, and aggregate pain and quality of

life survey scores at the first post-operative visit. . Patient participation is concluded following the first post-operative visit

Patient participation will be terminated if any adverse reaction to the study medication is noted.

g) Procedures Involved in the Human Research

Study subjects will undergo breast surgery by the individual surgeon's standard technique. No changes in surgical technique will occur as part of this study. Regional nerve block with bupivacaine and/or lidocaine is typically offered to patients as part of this procedure and is considered standard of care. However, not all patients opt to receive a nerve block

For the study, subjects will be randomized to experimental and control groups in a ratio of 1:1. Randomization will occur upon enrollment in the study. When the patient is enrolled, the investigator will use the Sealed Envelope™ simple randomization tool to assign the subject a treatment group. Randomization occurs in random permuted blocks to achieve an even distribution between groups. Patients will be blinded to their study group.

All subjects will receive perineural nerve block in the preoperative holding area prior to the case performed by faculty from the anesthesia pain service. An ultrasound guided pecs block will be performed. For the block, the fascial plane separating the pectoralis major and pectoralis minor muscles is identified by ultrasound at the level of the 3rd rib. A needle is advanced into this space and the local anesthetic is infiltrated. The experimental group will receive 29cc 0.5% bupivacaine mixed with 1mL 4mg/mL dexamethasone for each side (40 cc total). The control group will receive 29cc 0.5% bupivacaine mixed with 1mL 0.9% saline solution for each side.

All patients will undergo standard breast reduction with no change in the standard operative technique.

All patients will receive a standard postoperative pain regimen as follows:

- Percocet 5/325 1 tab q4hr prn pain (moderate, 4 – 7)
- Percocet 5/325 2 tabs q4hr prn pain (severe, 8 – 10)
- IV 1mg Morphine q1hr prn breakthrough pain
- IV 4mg Zofran q8hrs prn N/V

This may be adjusted for patient drug allergies

Bupivacaine is a local analgesic used routinely during surgical procedures. It is FDA approved for this indication.

Dexamethasone is a glucocorticoid available in oral and intravenous formulations. It is FDA approved for a multitude of anti-inflammatory indications. While off label, it is standard of care to provide IV

dexamethasone to prevent post-operative nausea and vomiting. It has not been evaluated by the FDA as an adjunct to local anesthesia.

Pain VAS scores are routinely collected by nursing staff and entered into Epic. We will request pain evaluations at 4 hour intervals for study patients following surgery which will be entered into the Epic medical record. Medication administration is also captured in the electronic medical record. Study data will be gathered from the Epic electronic medical record.

Patients will be asked to complete the MD Anderson Brief Pain Inventory Short Form and both the Breast-Q or the SF-36 questionnaire at their first post-operative visit.

As previously stated, regional block with bupivacaine alone is routinely offered and provided to patients. Patients who do not consent to participate in the study will be offered a regional nerve block containing only bupivacaine. Anesthesia pain service faculty will perform the block regardless of study participation or study group.

h) Data and Specimen Banking

Data will be collected and stored in an electronic database stored on the encrypted hospital network. All data will be stored in a password protected and encrypted manner.

Identifying patient information including name, date of birth, and medical record number and the associated study ID will be stored in a password protected document accessible only to the PI and study coordinator.

A separate database containing the de-identified study ID number and all collected study data will also be stored in a password protected, encrypted file. This file will contain clinical information such as pain scores, narcotic use, and length of stay. This database will be accessible to all study personnel involved in administering the study.

The database containing identifying patient information will be destroyed upon completion of all data analyses. All patient medical records will be cleared of the study ID at this time. The deidentified database will be maintained indefinitely for potential ongoing analysis.

i) Data Management

Prior to data collection, patients will be randomized into 2 groups (control or experimental). An independent source will generate a master list of study IDs and associated randomization status. Patients will assigned within the master list and randomized accordingly per the master list.

Data will be extracted from the Epic electronic medical record. Consultation with medical informatics has been obtained to assist with development of an automated data collection mechanism. Data will be stored in a spreadsheet that allows for manipulation and analysis. Patient surveys will be conducted a week after the procedure and documented on paper and the responses will be manually inputted into an electronic database (REDCap). Survey responses (REDCap) will be matched to inpatient data measurements (Epic) through study ID numbers. The spreadsheet itself will be encrypted and will be stored exclusively on hospital network databases.

The two groups will be compared using a Student T test to evaluate for significant differences in the endpoints of each group.

A 2 mean 2 sided power analysis was conducted assuming the mean VAS difference between groups to be 1.5. A sample size of 30 in each group will have 81% power to detect a difference in means of 1.500 assuming that the common standard deviation in 2.000 using a two group t-test with a 0.050 two-sided significance level. We anticipate using larger numbers to power subgroup analysis.

Analysis between the two groups will involve a linear mixed effect model to compare the pain scales of the two groups over time. If vital signs are dissimilar at the beginning of the study, they will be controlled for prior to analysis. Pain medication requirement (determined by quantity of pills or mg used of same medication) will also be controlled within the analysis model. Adjustments to the pain score within the groups due to pain medication usage will be performed.

However, need for postoperative anti-emetic therapy is expected to be a somewhat rare event with similar means. In a similar power analysis with an expected group A mean of 0.5 doses and group B mean of 1 dose with standard deviation of 1, a sample size of 63 is required to reach significance. A somewhat large standard deviation is expected given the need for repeated dosing in those who do experience post-operative nausea

Similarly, length of hospital stay is expected to be similar between the two groups. The difference is generally expected to be between a “before lunch” or “after lunch” discharge on post-operative day 1. A two-group t test with a 0.05 two-sided significance level will be used to evaluate a difference in length of hospital stay. Therefore, a 2 mean 2 sided power analysis assuming group A mean hospital stay of 16 hours and group B mean stay of 18 hours with 4 hour standard deviation, a sample size of 63 is required to achieve 80% power with $p<0.05$.

j) Confidentiality

All patient data will be deidentified prior to storage. Data will be stored in an encrypted electronic database. Only study personnel will have access to this database. No one will be permitted to store the database on a personal device. The database will be stored exclusively on hospital network servers.

k) Provisions to Monitor the Data to Ensure the Safety of subjects

No significant risk is anticipated by the proposed study interventions. All of the medications are currently in routine use at this institution. All adverse events related to study medication will be evaluated by the primary investigator. A MIDAS report will be filed for any adverse event. If there are any occurrences, an interim summary of adverse events will be compiled at 1 month and provided to the IRB.

The study will be terminated immediately if study interventions result in subjects requiring intensive care interventions or death.

l) Withdrawal of Subjects

Subjects will be withdrawn from the study if there are any intraoperative surgical complications requiring deviation from standard technique.

Subjects may withdraw from the study at any time

11) Risks to Subjects

Regional nerve block is an optional component of the standardly performed breast reduction at this institution. Participation in the study does entail all the standard risks of this procedure. These are primarily bleeding or bruising at the injection site, nerve damage resulting in pain, numbness or weakness, infection, and

inadvertent systemic injection of the anesthetic. There is a very small risk of pneumothorax.

Primary additional risk to subjects compared to the standardly practiced block is allergic or adverse reaction to the study medication posed by the administration of dexamethasone. Adverse effects of this medication include behavioral disturbance, cardiac arrhythmia, hyperglycemia, and immune suppression. There is additional risk of increased postoperative pain due to deviation from standard nerve block procedure.

12) Potential Benefits to Subjects

Subjects may benefit from prolonged duration of local anesthesia resulting in enhanced postoperative pain control and decreased need for opiate analgesics.

13) Privacy and Confidentiality

All PHI will be removed prior to storage of any patient information. PHI will not be shared with any research personnel or any other persons. Randomization status and all medications received will be disclosed to all healthcare personnel involved in the patient's care while in the hospital. The patient will not be informed of his or her study group.

Patients will be completely informed of all privacy procedures as part of the consent process. Study personnel will be available to answer questions throughout the duration of the study.

14) Compensation for Research-Related Injury

No compensation is available for research related injury

15) Economic Burden to Subjects

Subjects will not incur any costs by participating in this study

16) Consent Process

- Consent will be obtained following "INVESTIGATOR GUIDANCE: Informed Consent (HRP-802)."
- The study will be described in full to the patient during the pre-operative clinic visit. The patient will be provided with the consent form at this time for review. If the patient is agreeable, written consent for the study will be obtained at this time.
- Separate standard procedural consents will be obtained for the surgery itself and the regional nerve block as per current practice. These will be obtained by the operating surgeon and anesthesiologist respectively.

- Study personnel will again explain the details of the study to the patient upon arrival in the pre-operative holding area. The patient will be given to opportunity to ask questions and participation in the study will be confirmed prior to leaving the holding area.

Non-English Speaking Subjects

- Spanish speaking subjects are also eligible for participation in the study. Consent will be obtained using a Hospital-approved official interpreter
- Subjects and the official interpreter will sign the Spanish Short Form consent after the full consent has been verbally translated to the subject
- Patients who speak neither English nor Spanish are excluded

Subjects who are not yet adults (infants, children, teenagers)

- Minors will be excluded from participation in the study

Cognitively Impaired Adults

- Capacity to consent will be determined by the operating physician
- Cognitively impaired adults are excluded from participation

Adults Unable to Consent

- Adults unable to consent will be excluded

17) Process to Document Consent in Writing

Written consent will be obtained per "INVESTIGATOR GUIDANCE: Documentation of Informed Consent (HRP-803)."

Vulnerable Populations

Prisoners, pregnant women, minors, and adults unable to consent are excluded form participation in the study

18) Drugs or Devices

No non formulary drugs or devices are used in the study. All study medications will be stored per hospital pharmacy protocols

19) Sharing of Results with Subjects

Subjects will not receive individual results of this study