PROTOCOL **NCT03187080**

Title: Enhanced Recovery Strategies in Elective Breast Surgery

Protocol:
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PI: Venkat Rao, MD, MBA[1]
Professor of Surgery, Division of Plastic Surgery

Affiliation:
Department of Surgery-Division of Plastic Surgery
University of Wisconsin School of Medicine and Public Health
G5/350 Clinical Sciences Center
600 Highland Ave
Madison, WI 53792

Project Summary

Postoperative pain, nausea, and vomiting are frustrating sequelae of elective breast surgery. Poorly managed postoperative pain can lead to increased opioid use, increased postoperative nausea and vomiting (PONV), delayed return to work and usual activities, unplanned hospital admissions, surgical complications, and patient dissatisfaction. In light of the growing opioid epidemic in the United States, any intervention that potentially minimizes opioid use may have meaningful individual and societal impact. In patients undergoing breast reduction and breast augmentation surgery, multiple techniques for managing postoperative pain are used commonly. One such technique is the use of a paravertebral block (PVB), which is a method of injecting local anesthesia into the area surrounding the spinal nerves in order to decrease sensation and pain in the chests and breasts in the setting of breast surgery. PVB is generally used concomitantly with standard multimodal perioperative pain management including cool compress, non-steroidal anti-inflammatories (NSAIDs), acetaminophen, and opioids. All of these pain management strategies are used at the University of Wisconsin and are considered standard of care for breast surgery nationwide.

The overall purpose of this study is to evaluate interventions that aim to optimize pain control, minimize the risk of PONV, and improve recovery after elective breast surgery. We will do this by (1) Comparing PVB with standard pain management strategies in patients undergoing planned breast reduction and breast augmentation, and (2) Comparing "enhanced recovery" strategies to standard of care for patients undergoing planned breast reduction and breast augmentation. This will be studied using pain assessments, validated surveys, medication logs, and review of medical records.

Background and Significance

Bilateral breast reduction and bilateral breast augmentation are both routine plastic surgery procedures commonly performed on an outpatient basis. While patient satisfaction following these procedures is high, postoperative pain management can be challenging, resulting in decreased patient satisfaction, delayed recovery including delayed return to work and daily activities, increased opioid pain medication requirements and occasionally unplanned hospital admissions, surgical complications, and increased cost of care [Davis].

PVB is a common procedure used for analgesia in breast surgery in combination with multimodal perioperative pain regimens, though its use has not been formally studied in a prospective fashion. Our Division recently retrospectively studied the use of PVB in breast reduction, finding that postoperative pain scores and rates of PONV were decreased with the use of PVB. To date, no prospective, randomized, blinded study has been performed to evaluate the efficacy of PVB on perioperative pain management in this patient population. Multiple studies performed in patients undergoing post-mastectomy breast reconstruction have demonstrated the safety and efficacy of PVB as an adjunctive pain control modality. In a prospective study evaluating patients undergoing post-mastectomy autologous breast reconstruction, Parikh and colleagues found that patients who received PVB had significant improvement in postoperative pain, shorter time to oral-only opioid usage and decreased length of hospital stay compared to patients who received standard postoperative pain control [Parikh]. A meta-analysis conducted by Schnabel and colleagues studied 15 randomized controlled trials evaluating PVB in addition to general anesthesia for patients undergoing breast surgery found significant decrease in postoperative pain scores with low risk ratio for adverse events [Schnabel].

The concept of "enhanced recovery" or "fast track" surgery was borne out of several prospective studies in the gastrointestinal surgery literature, and has been shown in multiple types of operations and across specialties to be beneficial for patients as well as economically advantageous [Anderson, Bonde, Adamina]. The concept of using an integrative, multimodal, multidisciplinary approach for minimizing the physiologic stress response in attempt to improve recovery after surgery was first described in 1997 [Kehlet]. Throughout the past several years there has been increasing focus on applying such principles to breast surgery, though to date the literature has focused on operations primarily performed for breast cancer, including mastectomy and breast reconstruction [Arsalani, Bonde]. The goal of "enhanced recovery after surgery" (or "ERAS") protocols is to identify and employ a set of pre-, peri- and postoperative strategies to improve patient outcomes and the recovery process after surgery. Such interventions have the goal of minimizing perioperative physiologic stressors (e.g. pain, fatigue, anxiety, nausea and vomiting) that can lead to morbidity. Categories related to "enhanced recovery after breast surgery" (ERABS) include standardized preadmission counseling, preoperative fasting, preanesthetic anxiolytics, anesthetic protocols, intraoperative warming, pain control, prevention of nausea and vomiting, mobilization, and postdischarge support [Arsalani].

Thus, the overarching goal of this study is to evaluate the safety and efficacy of PVB alone, as well as in conjunction with a global set of perioperative enhanced recovery strategies in elective breast surgery. We hypothesize that the use of such strategies will improve the patient experience of breast reduction and augmentation beyond the current standard of care.

We are conducting this study because, to our knowledge, no previous study has prospectively evaluated the use of PVB (with or without additional ERAS strategies) in groups comprised only of patients undergoing non-oncologic breast surgery. We hypothesize that the use of PVB in breast reduction and breast augmentation may be as beneficial as it has been shown to be in patients undergoing lumpectomy or mastectomy and subsequent reconstruction. In addition, no other study, to our knowledge, has prospectively studied enhanced recovery strategies (with PVB) in elective breast surgery (including reduction and augmentation). Due to the physical and psychosocial differences in patients undergoing elective breast surgery (compared to oncologic breast surgery), we wish to study elective breast surgery to better understand the effects of ERABS strategies on postoperative pain, nausea, and overall patient recovery.

Experimental Design

There are **four** serial aims of this study. The overarching goal of the study is to prospectively assess the use of PVB as an adjunct for postoperative pain control both alone and in the setting of related ERABS strategies in elective breast surgery (both breast reduction and breast augmentation, two of the most common non-oncologic breast operations performed in an ambulatory setting). The methodologies used to assess postoperative pain, the set of collective ERABS strategies, the potential risks and benefits of study participation, and the inclusion/exclusion criteria will be the same in the groups studying breast reduction and those studying breast augmentation. As both operations are performed on a regular basis in the PI's practice, we feel it essential to evaluate both operations.

Following completion of all 4 groups, we will be able to assess the impact of PVB alone as well as the impact of ERABS strategies in both breast reduction and breast augmentation. We hope that this will help inform clinical conversations with patients and also guide clinical decision-making with respect to postoperative pain management and overall optimization of recovery in

elective breast surgery. We feel it important that the four distinct groups be included under the single protocol.

The primary aim in all four groups in this study is to evaluate postoperative pain scores in patients receiving either paravertebral block or ERABS strategies compared to patients who do not receive these interventions. Additional outcomes include use of analgesic and antiemetic medication, development of PONV, time to discharge, patients' assessment of quality of recovery as determined by a validated survey and overall patient satisfaction.

Research Design and Methods

Target population

i. Female patients undergoing elective breast reduction or breast augmentation by Dr. Venkat Rao, Dr. John Siebert or Dr. Katherine Gast at either Transformations Surgery Center or Madison Surgery Center (MSC).

Inclusion criteria

i. Age equal to and greater than 18 years.
ii. Medically cleared to undergo elective breast surgery (including associated anesthesia) at UW Transformations Surgery Center or Madison Surgery Center (MSC).
iii. iii. Undergoing bilateral breast augmentation or bilateral breast reduction by the PI or other participating attending surgeons (Dr. Rao, Dr. Siebert and Dr. Gast).

Exclusion criteria

i. Minors or under the age of 18
ii. Pregnant or breast feeding women
iii. Incarcerated women
iv. Males
v. Individuals unable to give consent due to another condition such as impaired decision-making capacity.
vi. Women who take opioid pain medications on a regular basis prior to surgery.
vii. Women with a history of opioid abuse and/or dependence.
viii. Women who, based on anesthesiologist discretion, are not candidates for paravertebral block.
ix. Women with BMI >40 (for PVB arm of study)
x. Women with a diagnosis of obstructive sleep apnea who are noncompliant with their treatment (e.g. CPAP use).
xi. Women with a history of bleeding disorders precluding safe paravertebral block.
xii. Women on anticoagulation therapy who have not held their anticoagulation as recommended by their surgeon or anesthesiologist.
xiii. Women with a history of infection at the site of paravertebral block.
xiv. Women not medically cleared for surgery at Transformations or MSC and thus would not be undergoing surgery at Transformations or MSC. This would include women with sepsis/bacteremia, significant valvular disorders or heart conditions.

Recruitment, Group Selection and Randomization Procedures:

Patients seeking breast reduction or augmentation who are seen by Dr. Rao, Dr. Gast or Dr. Siebert's office and meet all inclusion and exclusion criteria will be approached to participate in this study. Participation in this study is voluntary. Those patients interested in participation in this

study will be consented for participation per IRB approved process. The consent process will only be completed by study personnel who have completed the necessary training to do so.

Subjects are split into two groups: subjects undergoing breast reduction and subjects undergoing breast augmentation. Subjects undergoing breast reduction will be enrolled into either Group 1 or Group 3 of the study. Subjects undergoing breast augmentation will be enrolled in either Group 2 or Group 4. Regardless of the group in which the subjects are enrolled (e.g. Study Group 1, 2, 3, or 4), all subjects will be randomized to one of two treatment arms using a computer generated randomization table.

For groups 1 and 2, when a patient consents to participate in the PVB and sham PVB study groups they will be randomized in blocks of 10, so that for every 10 patients enrolled, 5 will be randomized to the PVB arm while 5 are randomized to the subcutaneous saline arm. All patients, regardless of study group / treatment arm, will undergo routine preoperative workup and management that all patients undergoing breast reduction or breast augmentation with Dr. Venkat Rao routinely undergo.

For groups 3 and 4, when a patient consents to participation in the ERABS or non-ERABS arms of the study they will be randomized in blocks of 10, so that for every 10 patients enrolled, 5 will be randomized to the ERABS arm while 5 are randomized to the non-ERABS arm. All patients, regardless of study group / treatment arm, will undergo routine preoperative workup and management that all patients undergoing breast reduction or breast augmentation with Dr. Venkat Rao routinely undergo.

Group Descriptions

Group 1: To prospectively determine the effect of PVB on perioperative pain and postoperative recovery following breast reduction. We will use patient-reported pain assessments (including a numeric rating scale) to evaluate our primary endpoint (pain scores on postoperative day 1 (POD1)) as well as additional outcome measures of pain scores in recovery and at 1 week post-surgery. To determine the effect of PVB on secondary endpoints of this study, we will calculate analgesic and antiemetic medication use, compare average time (minutes) spent in the PACU, average time (minutes) spent in Phase 2, total time (minutes) between the end of the operation and discharge to home, and evaluate the occurrence of unplanned hospital admission, PONV, overall satisfaction, patients' assessment of quality of recovery as determined by a validated survey [Gornall, Myles], and complications. This data will be obtained through review of medical records, surveys, and postoperative diaries.

Patients electing to undergo breast reduction will be invited to participate in the study at their preoperative visit. All patients choosing to take part in the study will be consented prior to their procedure. The study participants will be randomized to one of two arms within each Group using block randomization. Details of the allocated group will be written on a piece of paper and placed inside sealed, opaque, and sequentially numbered, envelopes. Block randomization will be performed using a computer-generated number list and an Excel spreadsheet template. Block randomization will ensure equal numbers of subjects in each group. Either the anesthesiologist or the surgical team will open the envelope when the patient presents to either UW Transformations Surgery Center or Madison Surgery Center (MSC) on the day of surgery. The subject will be randomized to receive either (a) standard postoperative nausea and pain control as well as a sham superficial injection of normal saline or (b) PVB in addition to standard postoperative nausea and pain control. PVB and sham superficial injections of normal saline will be performed by a trained

anesthesiology provider and will be performed in the routine manner. Surgery will take place in the usual fashion and participants will receive standard of care for pain and nausea control.

Following surgery, patients will be assessed for postoperative pain, nausea and vomiting. Assessment for postoperative pain will consist of a validated pain score survey administered prior to transfer to phase II postoperatively, on POD1, and at their one-week postoperative visit. Participants will also be asked to record, using a postoperative diary/log, when they take postoperative analgesics and antiemetics, which medications are taken, and quantity of medication taken. This will also be reviewed both in the medical record and upon discussion with the participant at the postoperative visits. Assessment of the time spent in the recovery room, time spent in Phase 2 of recovery, and time to discharge from the hospital (total time between the end of surgery to discharge from hospital), will be obtained via review of the medical record. At the first postoperative visit, participants will undergo a routine interview that includes discussion of their pain control, analgesic and antiemetic use, recovery process, and overall satisfaction. The medical record will be reviewed for any unplanned postoperative hospital readmissions related to the surgery.

Group 2: To prospectively determine the effect of PVB on perioperative pain and postoperative recovery following breast augmentation. We will use patient-reported pain assessments (including a numeric rating scale) to evaluate our primary endpoint (pain scores on postoperative day 1 (POD1)) as well as additional outcome measures of pain scores in recovery and at 1 week post-surgery. To determine the effect of PVB on secondary endpoints of this study, we will calculate analgesic and antiemetic medication use, compare average time (minutes) spent in the PACU, average time (minutes) spent in Phase 2, total time (minutes) between the end of the operation and discharge to home, and evaluate the occurrence of unplanned hospital admission, PONV, overall satisfaction, patients' assessment of quality of recovery as determined by a validated survey, and complications. This data will be obtained through review of medical records, surveys, and postoperative diaries.

The procedures will be the same as those described for Group 1, except patients will be undergoing planned breast augmentation.

Groups 3 and 4: To prospectively compare the standard of care for ambulatory breast surgery to "fast track" (also known as "enhanced recovery") strategies for breast surgery by assessing pain scores, pain medication and antiemetic use, development of nausea/vomiting, time to discharge, and patient satisfaction.

For the third serial Group in the study, patients electing to undergo breast reduction surgery will be invited to participate in the study at their preoperative visit. For the fourth Group in the study, all procedures will be the same as described in this section, but the patients will be undergoing breast augmentation surgery (not breast reduction). All patients choosing to take part in the study will be consented prior to their procedure. The study participants will be randomized, using block randomization, a computer-generated randomization template, and sealed, numbered, and opaque envelopes, to either receive (a) perioperative pain, nausea, and recovery strategies as part of our Enhanced Recovery after Breast Surgery (ERABS) protocol, or (b) perioperative instructions, anesthesia and medications as per our institution's current standard of care for elective breast reduction or breast augmentation. Subjects randomized to receive ERABS strategies will receive standardized written preoperative instructions. The Transformations or MSC staff will be aware of the study for these patient populations, and they will know which subjects are part of the study. When they call the patient they will remind them to follow instructions received prior to surgery.

In addition, following randomization, Transformations or MSC nursing staff will receive written information (in an envelope) for that subject. This will be kept in a file and the envelope will be opened when nursing staff calls the patient prior to surgery. The Transformations or MSC nurses calling the patient prior to surgery will not be blinded. For comparing ERABS strategies to our current perioperative standard of care, we will utilize the following perioperative strategies as specifically recommended by Arsalani et al:

- Provide written information about the surgical procedure, expectations, and postoperative care at the preoperative visit.
- Allow clear liquids up to 2 hours prior to arrival at the surgery center (rather than NPO at midnight).
- Multimodal pain control – Oral ibuprofen, acetaminophen; as needed opioids.
- Use of antiemetics (e.g. ondansetron).
- Early ambulation.
- Easily accessible call-in or walk-in postop care/support.

The proposed strategies differ from standard of care in the following ways:

- Patients do not eat or drink anything after midnight the morning of surgery.
- There is no standardized preoperative information packet.
- Anesthetic/intraoperative analgesic and antiemetic regimen varies between providers.

The following table outlines the proposed rapid recovery protocol, as adapted from Arsalani et al and Anderson et al [Arsalani, Anderson]:

	Enhanced Recovery / Optimized	Standard of Care
Prior to day of surgery	- Written, standardized information - Allowance of clear liquid diet up to 2 hours before arrival to surgery center	- No additional information - Nothing by mouth after midnight the night before surgery
Preop and Anesthesia - Premedication	- Midazolam and fentanyl for PVB - Acetaminophen 1000mg PO - Single dose of gabapentin 600mg PO - Meclizine 25mg PO	- +/- Midazolam - Acetaminophen
- Induction and maintenance	- Per anesthesiologist discretion (recommend total intravenous anesthesia when appropriate)	- Per anesthesiologist discretion
Intraoperative - Analgesia	- IV opioids per anesthesiologist discretion - Ketorolac 15mg	- IV opioids per anesthesiologist discretion

- Antibiotic prophylaxis - DVT prophylaxis - Antiemetics - Drains	- One time dose before incision - SCDs +/- chemoprophylaxis if indicated - Dexamethasone during induction 4-5mg - Ondansetron just prior to emergence - Drains always removed POD1	- One time dose before incision - SCDs +/- chemoprophylaxis if indicated - Per anesthesiologist discretion - Drains usually removed POD1
Postoperative - Medications - Mobilization	- Phase I/II as needed opioids or other analgesics - Discharge prescriptions: Scheduled acetaminophen, scheduled ibuprofen or naproxen, scheduled for 5 days, as needed oral opioid - Scheduled ondansetron for 48 hours, then as needed - Ambulate prior to discharge	- In Phase I/II per anesthesiology discretion - On discharge per surgeon discretion

Following surgery, patients will be assessed for postoperative pain, nausea and vomiting.

We will use validated pain assessments to evaluate our primary endpoint (pain scores on postoperative day 1 (POD1)) as well as additional outcome measures of pain scores in recovery and at 1 week post-surgery. To determine the effect of PVB on secondary endpoints of this study, we will calculate analgesic and antiemetic medication use, compare average time (minutes) spent in the PACU, average time (minutes) spent in Phase 2, total time (minutes) between the end of the operation and discharge to home, and evaluate the occurrence of unplanned hospital admission, occurrence of PONV, assessment of recovery, overall satisfaction, and complications. This data will be obtained through review of medical records, questionnaires, and postoperative diaries.

PVB Procedure Details

Historically, PVB has not been routinely performed at Transformations. However, many other types of regional anesthetic techniques have been and are being performed at Transformations on a routine basis, and all members of the perioperative team (nursing staff, anesthesiologists, and surgery team) understand the risks of local anesthetics and the facility is equipped and prepared to address potential complications. With respect to PVB, a formal inservice will be held prior to subject recruitment for this protocol. This inservice training will be unrelated to this study, as Transformations staff is planning to increase the frequency with which perioperative blocks are performed for various types of surgeries, similar to what is currently done at Madison Surgery Center and The American Center.

All PVBs will be performed using an out-of-plane ultrasound approach by an anesthesiologist with appropriate training in regional anesthesia. An in-room anesthesiologist or regional fellow who has been trained to perform PVB may perform the PVB; when each fellow demonstrates competence in regional blocks they are able to start performing them independently and staffing residents doing them. Once deemed competent, while working at UWHC, TAC, and TSC for the year of their fellowship, they are performing blocks and/or staffing residents within the scope of their standard clinical practice. If the optics of the blocks are not optimal, the anesthesiologist will abort the block as per their standard clinical practice in any other situation.

The PVB may either be performed preoperatively or intraoperatively. The patient will be placed in a seated position with shoulders slumped and body slightly flexed forward. Standard ASA monitors will be applied. A time-out procedure will be performed to confirm patient, allergies, and procedure. The patient and surrounding care providers will not be informed regarding whether paravertebral block or subcutaneous saline injection is being performed. The anesthesia provider performing the injection will be the only person informed regarding the use of PVB with local anesthetic or subcutaneous saline injection. The site will then be marked to confirm nerve block location.

Landmarks on the patient will be palpated, identified, and marked. The skin will be sterilized. The ultrasound probe will be positioned in a parasagittal/cranial-caudal orientation approximately 2-3 cm lateral to the spinous processes on the operative side(s). The probe will be tilted laterally as needed to optimize viewing the parietal pleura by bringing it into a perpendicular orientation to the ultrasound beam. The intended target (paravertebral space) will be located between the transverse processes, just beneath the superior costotransverse ligament or internal intercostal membrane but superior to the parietal pleura.

A Pajunk UniPlex NanoLine needle (Pajunk, Geisingen, Germany) will be inserted into the patient. A 10-20 mL syringe filled with sterile, preservative-free normal saline (used for hydrodissection) connected via a stopcock to a 20-30 mL syringe of 0.25% bupivacaine with 2.5 mcg/mL of epinephrine will be connected to the Pajunk needle and used for injection. Depending on operator preference, needle insertion will be either medial-to-lateral or lateral-to-medial relative to the ultrasound probe. 1-2% lidocaine will be used to first anesthetize the skin before insertion of the Pajunk needle. The needle will be slowly advanced toward and through the superior costotransverse ligament or internal intercostal membrane. The normal saline will be used to hydrodissect the tissues in order to estimate needle position, as this is an out-of-plane approach and the needle is not easily visualized. To prevent air entrainment in the event of a pleural puncture, a continuous connection from the Pajunk block needle to the fluid filled syringe will be maintained. Once through the ligament, the pleura (which moves with inspiration) will be seen deflecting anteriorly with the saline hydrodissection. Negative aspiration will be confirmed,

and the local anesthetic will be injected incrementally into the paravertebral space. During injection, the depth between the transverse processes and parietal pleura should increase.

These will be bilateral PVBs. Patients weighing at least 40kg will receive approximately 40mL of 0.25% bupivacaine with 2.5mcg/mL epinephrine. This will be divided into 4 separate injections of approximately 10mL per level, 2 injections placed on each side. Targeted levels will be T 1-2/2-3 and T 4-5/5-6 with 2 levels separating the injection levels. Patients undergoing subcutaneous injection of saline will have a similar procedure performed as described above for PVB. However, instead of infiltration of normal saline and local anesthetics into the paravertebral space, 2-5ml of sterile injectable saline will be injected subcutaneously.

For when the PVB is performed preoperatively, ten to fifteen minutes after block placement, the dermatome levels will be checked using ice. If the block is not effective, this will be noted. Data will be analyzed using intention to treat principle. Any adverse event related to PVB will be handled in the same manner that is standard clinical practice at Transformations or MSC. Local anesthetics are used frequently at both Transformations & MSC and lipid emulsion is available. Local anesthetic toxicity may occur in the setting of tumescence with or without liposuction, other blocks in addition to PVB, or intraoperative field infiltration before or after surgery (e.g. in the setting of a miscalculated bupivicaine dose). In the event of any emergency, EMS is called and the patient would be transported via ambulance to UW Hospital.

Subcutaneous saline injections will be performed in the same manner as described above for PVB, however instead of injection of local anesthetic into the paravertebral space, an injection of sterile injectable saline into the subcutaneous plane will be performed. All other procedural aspects will be similar to that performed for PVB.

Breast reduction or breast augmentation will be performed in the standard fashion, and all patients will receive routine management as deemed appropriate by the surgeon and anesthesiologist regardless of treatment arm. Postoperatively, all patients will proceed to the recovery room/PACU, where they will receive routine postoperative cares, including standard ASA monitoring, and availability of analgesics and antiemetics. Prior to transfer from PACU to Phase II, all patients will be asked to assess their pain, including rate their pain on a 0 to 10 numeric rating scale (where 10 is associated with the “worst pain ever” and 0 is associated with no pain).

Each participant will be transferred from PACU to Phase 2 when she meets standard requirements for transfer. Similarly, patients will be discharged home when all discharge criteria have been met. All other postoperative patient care will be routine for all patients undergoing breast reduction or breast augmentation.

Statistical Methods

Our primary outcome of interest is postoperative pain scores in the two arms in each of the different study Groups, specifically in Group 1 (Breast reduction: Sham block versus Breast reduction: PVB), Group 2 (Breast Augmentation: Sham block versus Breast Augmentation: PVB), Group 3 (Breast reduction: Standard of care versus Breast reduction: Enhanced Recovery Strategies), and Group 4 (Breast Augmentation: Standard of care versus Breast Augmentation: Enhanced Recovery Strategies).

Thus, this study is comprised of four distinct Groups for which the outcome metrics are the same. We reviewed previously published prospective studies prior to performing a power calculation to identify a sample size. Kairaluoma et al randomized 60 patients who were undergoing oncologic

breast surgery to either general anesthesia + PVB (n=30) or general anesthesia + sham block with saline (n=30). The subjects in the PVB group had a significantly lower opioid requirement in PACU, less PONV in PACU ($p=0.05$), and lower pain scores 24 hours after surgery ($p<0.01$).

In a study of 60 patients with 30 patients per group, Dabbagh and colleagues randomized subjects to receive general anesthesia or PVB. The subjects underwent "elective breast surgery" but the authors did not specify the type or laterality of the operations. Patients in the PVB group had better postoperative pain scores in recovery ($p<0.0001$), fewer morphine requirements ($p<0.0001$), and earlier time to discharge ($p<0.0001$).

Finally, in a third study evaluating the efficacy of PVB in patients undergoing oncologic and elective breast surgery, 60 patients were assigned to receive PVB (n=30) or no PVB (n=30). Verbal postoperative pain scores were lower in the PVB group at 30 minutes, 1 hour, and 24 hours (all $p<0.05$). Nausea was found to be less in the PVB group at 24 hours ($p=0.04$) [Klein].

Based on means and standard deviations reported in the Klein study, we anticipate that, for each of the four groups, in order to have at least 80% power for finding significant differences, we will enroll 37 subjects per arm, for a total of 74 subjects per group. This power calculation is based on a two-tailed, two-sample t-test performed at a significance level of 0.05. Our primary outcome of interest is self-reported pain (0-10 visual analog scale) on post-operative day 1 (POD1). Additional outcomes of interest include pain scores in PACU/recovery area, time spent in each phase of care prior to discharge, time to discharge to home, analgesic requirements both in recovery and at home, post-operative nausea and vomiting, antiemetic usage, and complications. Data will be analyzed using t-tests (with or without Satterthwaite adjustment) and Fisher's exact tests.

There will be 296 patients enrolled in the study (74 in each group, with four total groups that each have two arms) and therefore the medical record for 296 patients will be accessed to determine basic demographic information (age, BMI, smoking status, history of PONV), analgesic use, antiemetic use, time spent in PACU, time spent in phase 2, total time from end of surgery to discharge from surgery center, and postoperative complications.

Data and Safety Monitoring Plan

1. Summary of the Protocol: Please see the beginning of this protocol document for study design and procedures, as well as primary and secondary outcome measures.
2. Roles and Responsibilities
    a. The principal investigator, Dr. Venkat Rao, will be responsible for monitoring the trial. Dr. Rao is a Professor of Surgery and the study is taking place under his supervision. Any adverse events will be reviewed promptly and reported to the IRB per current guidelines.
    b. Resident Physicians &/or future study team members who may assume a study coordinator role in the Department of Plastic Surgery, will be responsible for monitoring data collection, adverse events, and protocol deviations. Reportable events will be submitted per current guidelines.
3. Data and events to be captured
    a. Study members will be collecting basic demographic information via chart review on all patients enrolled in this study. This will include patient age, BMI, medical comorbidities, smoking status, history of PONV.
    b. Study members will also be collecting data during the peri-operative period that is pertinent to the study. This will include time in each phase of care, total narcotic use in PACU, survey results from PACU, POD 1 and POD 7.

c. All adverse events, complications related to the procedure(s) performed as part of the study, deviations from the protocol will also be collected.

4. Data Management, Analysis, and Quality Assurance:
    a. Identification of data sources (e.g., questionnaires, medical records, biospecimen collections, audio/video recordings)
        i. Data sources for this study include:
            1. Medical record review
            2. Questionnaires
            3. Postoperative diaries
    b. Frequency of Data Analysis
        i. For each group studied, data will be analyzed using statistical methods described above approximately every 20 patients that complete the study. This will allow for analysis of equal numbers of experimental arm vs. control arm while permitting evaluation for safety while the study is taking place.
    c. Description of the security measures in place to protect data sources including how the data will be labeled and stored.
        i. To protect against and minimize potential risks to confidentiality, all the information collected in this study will be coded and data will be kept in a locked office on a secure password-protected Department of Surgery server backed up by Surgery's internal IT team at the University of Wisconsin Hospital and Clinics Clinical Science Center. Hard copies of the consent forms will be stored in a locked filing cabinet in a locked office at the University of Wisconsin Hospital and Clinics Clinical Science Center. The information will only be made available to the study team members directly involved in the study. Confidentiality will be maintained by assigning a number to all subjects. The research subject log linking the name and subject number will be stored separately from the data and only authorized personnel will have access to the subject log. The PI and study staff will be alert for any breach of confidentiality.
5. Trial Safety:
    a. Description of any specific events that would preclude a participant from continuing the intervention
        i. All subjects will be given the opportunity to discontinue their participation in the study at any time.
        ii. Perioperatively, all subjects will be monitored using the same clinical practice standards that are applied to all patients undergoing surgery at Transformations or MSC. This includes monitoring for signs of local anesthetic toxicity, as well as complications of regional blocks.
    b. Description of the consent/assent procedures (e.g., by whom, how and under what conditions will a subject be consented).
        i. A study team member will obtain written informed consent prior to enrolling patients for participation in the study.
    c. Description of the mechanisms in place to protect subject privacy.
        i. Patient confidentiality will be ensured throughout the duration of this study. Discussing the protocol with the subject in a private room will help protect the subject's privacy. The collection of sensitive information will be limited to the amount necessary to achieve the aims of the research. The hard copies of the consent forms will be stored in a locked filing cabinet at the University of Wisconsin Hospital and Clinics Clinical Science Center. Confidentiality will be maintained by assigning

a subject number to all subjects. The research subject log linking the name and subject number will stored separately from the data, and only authorized personnel will have access to the subject log.

d. Description of the process for the disclosure of any conflicts of interest that may potentially challenge participant safety or bias the data and how the conflict will be managed.
    i. If any conflicts of interest arise that may challenge safety or bias the data, they will be immediately brought to the attention of the PI. If it is the PI with the conflict of interest, the study will be discontinued.
e. Description of the data security in place to protect the confidentiality of the data (e.g., password protected encrypted electronic records) and any limits to confidentiality.
    i. To protect against and minimize potential risks to confidentiality, all the information collected in this study will be coded and data will be kept in a locked office on a secure password-protected Department of Surgery server backed up by Surgery's internal IT team at the University of Wisconsin Hospital and Clinics Clinical Science Center. Hard copies of the consent forms will be stored in a locked filing cabinet in a locked office at the University of Wisconsin Hospital and Clinics Clinical Science Center. The information will only be made available to the study team members directly involved in the study. Confidentiality will be maintained by assigning a number to all subjects, and all data will be coded. The research subject log linking the name and subject number will be stored separately from the data and only authorized personnel will have access to the subject log. The PI and study staff will monitor closely for any breach of confidentiality.

6. Reportable Events:
    a. Description of the process and timelines (e.g., hours, days) for collecting and reporting Adverse Events (AEs), Serious Adverse Events (SAEs), and Unanticipated Problems Involving Risks to Subjects or Others to appropriate monitoring and regulatory entities (See NIMH Reportable Events Policy for definitions and timeframes).
    b. Adverse Events, Serious Adverse Events, and Unanticipated Problems will be immediately brought to the attention of the PI via email or telephone call (with plan for telephone call if no confirmed response to email) at any day or any time that the incident occurs. . Reportable events will be submitted per current guidelines.
        1. There are few rare side effects of PVB and if they occur, an adverse event would be reported.
            a. These side effects are rare:
                i. Bleeding and infection at the site of injection.
                ii. Low blood pressure.
                iii. Injecting local anesthesia into the wrong area including a blood vessel, and/or the space around the lungs.
                iv. Causing air to collect around the lung space.
                v. Nerve damage
                vi. Seizure
                vii. Cardiac arrest
        2. Regional anesthesia (such as paravertebral block) is commonly used modality for adjunctive analgesia and anesthesia in elective

breast surgery. At this time, PVB is more commonly performed at UW Hospital, due to availability of certified anesthesiologist providers. Regional anesthesia, including PVB, is one of many options in the surgeon's, anesthesiologist's, and patient's armamentarium for perioperative anesthesia and pain control. Regional anesthesia is performed at Transformations. The risks of PVB are not unique to Transformations all providers performing regional anesthesia have been specifically trained to do so.

3. Please note that there are no risks that are serious or irreversible that can be specifically related to participation in this study. As PVB is commonly performed in breast surgery cases, any risks attributable to PVB alone are not unique to this study, as patients undergoing the same procedure outside the study would have the same risks.
    a. The act of randomization may cause a patient to receive a less beneficial pain management or recovery protocol. However since surgery is currently performed both with and without PVB, as well as with and without elements of the enhanced recovery protocol, the risks are well within the standard risks of elective breast surgery. In addition, there are no late effects of paravertebral blocks.

7. Stopping Rules
    a. Upon evaluation of patient data as described above, if any statistically significant increase in morbidity or mortality is identified in the experimental group in comparison to the control group, study members will re-evaluate all results. If it is determined that a statistically significant increase in morbidity or mortality is attributable to patient participation in the experimental group, all patient recruitment will be halted and the IRB will be contacted via ARROW. The safety of continuing with the study will be further evaluated, and procession of study activities will be halted until IRB approval.

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