A COMPARISON OF PULSED ELECTROMAGNETIC FIELDS AND PECTORAL INTERFASCIAL BLOCKS ON POSTOPERATIVE PAIN REDUCTION IN PATIENTS UNDERGOING MASTECTOMY AND TISSUE EXPANDER RECONSTRUCTION

BACKGROUND

STUDY PURPOSE AND RATIONALE:

Provide pertinent background information with references that are related to the need to conduct this study. If this is a clinical trial, the background should include both preclinical and clinical data. Be brief and to the point.

The American Cancer Society estimates 230,000 new cases of breast cancer in 2015[1]. Rates of breast cancer are also increasing due to improved early detection as are the rates of mastectomy and prophylactic mastectomies. In patients treated with mastectomy, chronic post-operative pain is a well-described phenomenon [2]. A survey of 3253 women two to three years after surgical treatment for breast cancer found that 47% reported having some degree of residual pain, 13% of which was characterized as severe. Interestingly, severe acute postoperative pain after breast surgery has been shown to be a risk factor in the development of persistent and chronic pain in the long-term [3]. Thus, optimizing acute postoperative pain provides both short-term patient relief and holds significant potential in the prevention of long-term chronic pain [4]. Both pulsed electromagnetic field (PEMF) devices and pectoral interfascial blocks (PIB) have been shown to be effective analgesic modalities for breast surgery [5, 6] and both are currently in use at Columbia University Medical Center (CUMC). We have previously reported the efficacy of PEMF devices in reducing postoperative pain, and narcotic use following TRAM flap breast reconstruction. In addition, the PEMF devices in our previous TRAM study have been shown to significantly reduce pro-inflammatory cytokine levels in the surgical bed, suggesting that it has beneficial effects on wound healing [7]. Currently, there is no literature on PEMF or PIB use in mastectomy and tissue expander breast reconstruction patients, and nothing comparing the efficacy of the two modalities on postoperative pain. We propose a prospective, randomized, controlled double-blind trial to evaluate the efficacy of PEMF and PIB in controlling postoperative pain in mastectomy and tissue expander patients.

STUDY DESIGN

Describe the methodology that will be used in this study, covering such factors as retrospective vs. prospective data collection, interventional vs. non-interventional, randomized vs. non-randomized, observational, experimental, ethnography, etc.

We propose a prospective randomized controlled double-blind interventional study comparing the effect of pulsed-electromagnetic field device (PEMF), pectoral interfascial block (PIB), and placebo on postoperative pain control. This study has the interdisciplinary cooperation of the regional anesthesia group, and the breast and plastic surgery divisions. All female patients with breast cancer evaluated at CUMC who are undergoing unilateral or bilateral mastectomy with tissue expander reconstruction will be offered enrollment in this prospective study. Patients must be 18 years of age or older. Exclusion criteria include patients who are allergic to all narcotic medications, those who take opioids or pain medications for a chronic condition or chronic use preoperatively and medical record specifically states the chronic condition, and those who do not possess the capacity to make medical decisions for themselves.

RANDOMIZATION

The surgeons, all health-care personnel involved in the trial, the research coordinator, and all patients will be blinded. We have identified two volunteers who are not involved in the study in any way and share a locked office. This guarantees that a volunteer will be available on the day of surgery. They will create randomization envelopes based on the following randomization scheme:

Active PEMF + Treatment PIB	Active PEMF + Sham PIB
Sham PEMF + Treatment PIB	Sham PEMF + Sham PIB

The volunteers will:

- Create a randomization list with four arms (15 subjects in each arm) using this link: **https://www.random.org/lists**
- Create 60 sequential envelopes and place a paper with the assignment based on the randomization list.

The sequential randomization envelopes will be kept in the volunteer's locked office. Bupivacaine/Ropivacaine will be stored in the NYPH 4th Floor Pharmacy. On procedure day:

- One of the volunteers will retrieve a sequentially numbered and sealed randomization envelope and will retrieve the study drug from the NYPH pharmacy and hand it to the study physician;
- The study physician will draw up both saline (sham PIB) and Bupivacaine/Ropivacaine (treatment PIB) and label the syringes with the patient's name, MRN, the medication that was drawn up and the date and time of preparation. This will take place in the pre-op area.
- The volunteer will bring both syringes to a location away from the pre-op area and refer to the randomization envelope to learn the assignment. She will remove the label that was affixed by the study physician and affix a new label with patient name, MRN, STUDY DRUG VS PLACEBO. The date and time of preparation will be hand-written on the appropriate treatment arm syringe (because this will not be known until the syringes are retrieved.

The unused syringe will be disposed of appropriately by the volunteer. To ensure both the healthcare professionals and patients are fully blinded, on the day of surgery, all patients will receive an ultrasound-guided injection of either saline (sham PIB) or Bupivacaine/Ropivacaine (treatment PIB), and all patients will wear postoperative bilateral PEMF devices (some of which will be sham devices visually identical to the active devices. The PEMF devices (Ivivi Health Sciences, LLC) are FDA approved for pain and edema relief, and we will be using the devices for their FDA-approved purpose. Bupivacaine/Ropivacaine is an FDA approved local anesthetic currently used in pectoral interfascial blocks for breast surgery patients. All patients will receive standard post-operative pain medications as needed.

We are planning an initial cohort of 60, with 15 subjects per treatment arm. As such, 30 subjects will wear a sham PEMF device while another 30 patients will wear real PEMF devices.

Table 1. Treatment Arms

Active PEMF + Treatment PIB	Active PEMF + Sham PIB
Sham PEMF + Treatment PIB	Sham PEMF + Sham PIB

Postoperative care will be standardized with patient-controlled analgesia (PCA) for the first 24 hours, followed by oral narcotic medication. In the early postoperative period, pain levels and recovery status will be periodically

assessed using a standard, validated and tested tool—the visual analog scale (VAS) and quality of recovery (QoR) questionnaire respectively. Patients will be asked to assess their pain level and recovery status using VAS and QoR questionnaires respectively at standard time points: 1 hr (+/- 20 minutes), 3 hrs (+/- 20 minutes), and 5 hrs (+/- 20 minutes) postoperatively, and then asked for their maximal pain level everyday during waking hours from 7 am to 9 pm until the day of discharge.
Once discharged, patients will be asked to assess their pain level and quality of recovery everyday via a telephone call everyday between 7 am to 9 pm until their first follow-up appointment at 1 week postoperatively. Patients will be seen at 1 week (+/- 4 days) and 3 weeks (+/- 7 days) post operatively and asked to assess their pain level and recovery status using VAS and QoR questionnaires.

Data collection will include patient factors such as demographics, comorbidities, smoking status, operative factors including number of lymph nodes taken (if any), intraoperative analgesia consumption, type of mastectomy and reconstruction, type and size of expander, and postoperative factors such as opioid and narcotic use, nausea/vomiting, time to discharge, pain level using the visual analog scale (VAS) and recovery status using quality of recovery (QoR) questionnaire.

Primary outcome will be the rate of reduction of postoperative pain as quantified by VAS.

STATISTICAL PROCEDURES

Using our previous placebo-controlled study for the effect of PEMF [6] and prior literature comparing placebo to PIB [5], we determined that a sample size of 48 (12 per group) was necessary to ascertain a clinically meaningful difference in pain level with a statistical power of 80%. We plan to enroll 60 patients overall to compensate for dropout. Interim analysis will be performed by unblinded research team members when at least 30 patients have been accrued, completed follow–up visits and are off study. Preliminary analysis before the final data analysis will be performed by unblinded research team members when 51 patients have been accrued, completed follow-up visits and are off study. Final data analyses will be conducted in consultation with a biostatistician who will consult on appropriate tests for evaluating the normality of data and for performing comparative regression analyses of the data.

RECRUITMENT AND CONSENT

RECRUITMENT

Describe how participants will be recruited

Recruitment will take place during patients' scheduled consultations with the breast surgeon or plastic surgeon. Patients who present for mastectomy will be given the standard discussion of all breast reconstruction options. After this, patients who decide to have tissue expanders placed will be asked to participate in this study. Informed consent will be obtained. Throughout this, patients will be given opportunities to ask questions at any time during the enrollment and study and will be informed that they can decline to participate or drop out of the study at any time. After the informed consent is signed, the patient will be randomized into one of 4 groups—placebo (sham PEMF + sham PIB), active PEMF +sham PIB, PIB + sham PEMF, or active PEMF and PIB (Table 1).

RESEARCH AIMS AND ABSTRACTS

RESEARCH QUESTION(S)/HYPOTHESIS(ES)

Aim 1: To quantify the effect of PEMF devices on postoperative pain in mastectomy + tissue expander patients

Rationale: Prior studies have demonstrated the ability of PEMF devices to afford a significant reduction in postoperative pain for patients undergoing breast reduction or TRAM flap breast reconstruction. The proposed study seeks to establish whether PEMF is similarly efficacious in reducing postoperative pain in mastectomy + tissue expander patients.

Hypothesis: Mastectomy + tissue expander patients randomized to an active PEMF device and sham PIB will have significantly decreased postoperative pain as measured by VAS score compared to the sham PEMF and sham PIB group.

Aim 2: To evaluate the effect on PEMF devices on postoperative narcotic requirements

Rationale: In our previous double-blind, placebo-controlled, clinical study in breast reduction patients, we reported a two fold decrease in the use of postoperative narcotics when PEMF devices were used. As increased narcotic usage can have a host of side effects and delay healing, the proposed study seeks to evaluate the ability of PEMF devices to reduce postoperative narcotic requirements in mastectomy + tissue expander patients.

Hypothesis: Patients undergoing mastectomy + tissue expander placement randomized to active PEMF and sham PIB will have significantly reduced postoperative narcotic requirements as compared to the group randomized to sham PEMF and sham PIB.

Aim 3: To compare the efficacy of PEMF vs. PIB in the control of post-operative pain in mastectomy + tissue expander patients.

Rationale: Our prior studies have evaluated and demonstrated the efficacy of PEMF devices in reducing post-operative pain and pro-inflammatory cytokines for patients undergoing breast reduction or TRAM flap breast reconstruction. The current study seeks to compare the efficacy of PEMF devices and PIB on postoperative pain in mastectomy + tissue expander patients.

Hypothesis: Because the PEMF device is worn continuously after surgery for 7 days whereas the PIB is a one-time preoperative injection of local anesthetic, we hypothesize that mastectomy + tissue expander patients randomized to active PEMF devices and sham PIB will have significantly decreased postoperative pain as measured by VAS score when compared to the sham PEMF and treatment PIB group.

SCIENTIFIC ABSTRACT

In patient's treated with mastectomy, chronic post-operative pain is a well-described phenomenon [2]. A survey of 3253 women two to three years after surgical treatment for breast cancer found that 47% reported having some degree of residual pain, 13% of which was characterized as severe. The relief of acute postoperative pain holds significant potential in the prevention of such chronic pain [4]. Both pulsed electromagnetic field (PEMF) devices and pectoral interfascial blocks (PIB) have been shown to be effective analgesic modalities for breast surgery [5, 6].

Currently, there is no literature on PEMF or PIB use in mastectomy and tissue expander patients, and nothing comparing the efficacy of the two modalities on postoperative pain. We propose a prospective, randomized, controlled double-blind trial to evaluate the efficacy of PEMF and PIB in controlling postoperative pain in mastectomy + tissue expander patients.

A total of 60 patients will be randomized to four groups consisting of: active PEMF + treatment PIB, sham PEMF + treatment PIB, active PEMF + sham PIB, and sham PEMF + sham PIB. Data collection will include demographics, comorbidities, smoking status, operative factors including number of lymph nodes taken (if any), intraoperative analgesia consumption, type of mastectomy and reconstruction, and postoperative factors such as opioid and narcotic use, time to discharge, nausea/vomiting, pain level using the visual analog scale (VAS) and recovery status using the quality of recovery (QoR) questionnaire. The primary outcome between the groups will be reduction in pain level as assessed by the VAS. Reduction in VAS pain levels will then be compared between all four groups to evaluate the efficacy of PEMF vs. PIB on postoperative pain in mastectomy + tissue expander patients.

LAY ABSTRACT

Chronic pain after mastectomy, or breast tissue removal, is very common with almost half of women experiencing some type of residual pain and even 13% characterizing it as severe. Poor acute postoperative pain control is not only associated with development of chronic pain, but has also been shown to be associated with delayed wound healing. Therefore, optimization of postoperative pain control is paramount not just for patient comfort, but to decrease immediate and long-term postoperative complications. There are two adjunctive modes of perioperative pain control currently in use at Columbia University Medical Center (CUMC). The first mode uses pulsed electromagnetic fields (PEMF) and consists of a noninvasive device placed over dressings around the surgical site. The second is a regional anesthetic and —the pectoral interfascial block (PIB) in which a long-lasting local anesthetic (bupivacaine/ropivacaine) is injected into the surgical dissection area. Both of these techniques for postoperative analgesia have been shown to be effective in different types of breast surgery, but there is no current literature comparing the two modalities in their efficacy in reducing postoperative pain. There is also no current literature in their efficacy in the mastectomy and tissue expander patient population. The proposed trial is a prospective, randomized, controlled, double-blind trial to evaluate the efficacy of these two modalities of postoperative analgesia in patients undergoing mastectomy and tissue expander reconstruction.

A total of 60 patients will be randomized to four groups consisting of: active PEMF + treatment PIB, sham PEMF + treatment PIB, active PEMF + sham PIB, and sham PEMF + sham PIB. Data collection will include demographics, comorbidities, smoking status, operative factors including number of lymph nodes taken (if any), intraoperative analgesia consumption, type of mastectomy and reconstruction, and postoperative factors such as opioid and narcotic use, nausea/vomiting and pain level using the visual analog scale (VAS) and recovery status using the quality of recovery (QoR) questionnaire. The primary outcome between the groups will be reduction in pain level as quantified by the VAS. Reduction in VAS pain levels will then be compared between all four groups to evaluate the efficacy of PEMF vs. PIB on postoperative pain in patients undergoing mastectomy with tissue expander reconstruction.

RISKS/BENEFITS & MONITORING

POTENTIAL RISKS:

Provide information regarding all risks to participants that are directly related to participation in this protocol,

including any potential for a breach of confidentiality. Risks associated with any of the items described in the Procedures section of this submission should be outlined here if they are not captured in a stand-alone protocol. Risks of procedures that individuals would be exposed to regardless of whether they choose to participate in this research need not be detailed in this section, unless evaluation of those risks is the focus of this research. When applicable, the likelihood of certain risks should be explained and data on risks that have been encountered in past studies should be provided.

PEMF

The PEMF devices (Ivivi Health Sciences, LLC) are FDA approved for pain and edema relief, and we will be using the devices for their FDA-approved purpose. The pulsed electromagnetic field signal will consist of a 2-msec burst of 27.12-MHz radiofrequency sinusoidal waves repeating at 2 bursts/second [8]. Peak magnetic field was 0.05 G, which induces an average electric field of 4 ±1 V/m in each target site. The 18-cm coil produces a therapeutically useful signal up to 10 cm above and below the plane of the coil. This will ensure adequate depth of signal penetration (dose) for abdominal/chest wall, subcutaneous, and skin suture line pain. Sham devices will appear identical to and will be used in exactly the same manner as active devices but will produce no electromagnetic field. Both sham and active devices will have indicator lights that blink during pulsed electromagnetic field application. These pulsed electromagnetic field devices do not produce heat.

There have been no reported adverse or side effects in the 40 years that PEMF therapy has been used for recalcitrant fractures, chronic wounds, or post-operative pain relief [7, 9-11]. The primary investigator of the proposed study has extensive experience with these devices and has previously performed double-blind, placebo-controlled trials with breast-reduction patients without any adverse events.

PIB

Bupivacaine/ Ropivacaine is an FDA approved local anesthetic currently used in pectoral interfascial blocks for breast surgery patients. Bupivacaine and Ropivacaine are both long acting local anesthetics with a similar mechanism of action. The anticipated risks with the PIB and sham PIB interventions are those inherent in any injection, which includes bruising, hematoma, and the possibility of intravascular injection. PIB is already actively clinically utilized at CUMC and all patients will be informed of these risks during their informed consent with the option to forego this regional block. Regarding the sham PIB group, intramuscular 0.9% saline injections have been extensively reported in the anesthesia and orthopedic literature [12-14] and are widely regarded as a safe control without appreciable complications or risks to the patient.

POTENTIAL ADVERSE EVENTS RELATED TO THE STUDY

Potential adverse events related to the study might be local bruising at the injection site, skin reaction to the PEMF device and local anesthetic toxicity which will be determined by clinical assessment. However, local bruising is a minimal concern since these patients often have bruising from the mastectomy. These adverse events will be specifically collected for the study.

POTENTIAL BENEFITS

Provide information regarding any anticipated benefits of participating in this research. There should be a rational description of why such benefits are expected based on current knowledge. If there is unlikely to be direct benefit to participants/subjects, describe benefits to society. Please note that elements of participation such as compensation, access to medical care, receiving study results, etc. are not considered benefits of research participation.

The beneficial effects of PEMF devices on inflammation, pain, healing, etc. have been reported broadly and in a

growing number of fields [11, 15, 16]. Our own studies have demonstrated the dramatic reduction in postoperative pain in patients undergoing TRAM flap reconstruction or breast reduction. As such, patients randomized to the active PEMF device group may benefit from a similar reduction in postoperative pain. Patients in the placebo device group will likely not experience any benefit. Currently, PIB is used widely in CUMC for postoperative anesthesia and patients randomized to PIB may also gain an analgesic benefit [5]. There is no benefit anticipated from the sham PIB.

Despite the beneficial effects of PEMF demonstrated in prior studies, neither PEMF or PIB are widely used analgesic modalities at other institutions. If the proposed study demonstrates benefit for mastectomy and tissue expander reconstruction patients, these results may enable more generalized application of potential beneficial treatments for post-operative pain.

ALTERNATIVES:

If this research involves an intervention that presents greater than minimal risk to participants, describe available alternative interventions and provide data to support their efficacy and/or availability. Note, participants always have the option not to participate in research.

Patients can choose not to participate in this study and will undergo the same surgery with standard postoperative care and pain medication.

DATA STORAGE:

Provide a description of how the confidentiality of study data will be ensured, addressing concerns or protections that specifically relate to the data storage elements identified above (e.g. hard copy, electronic, system, and/or endpoint):

Information regarding patients enrolled in the study will be stored on a database on an encrypted drive. Only the investigators and research team of the study will have access to this information. Except for the enrollment log, patient's research data will be kept in separate database under a study ID number (which will include the serial number of the device), and not under the patient's name. Paper data such as consent forms, demographics, VAS score sheets, QOR questionnaires, etc. will be kept in a locked drawer in a locked office.

References

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