Title of Study: Intraoperative electrical stimulation of the acupoint P6 to prevent post-operative nausea and vomiting in women undergoing breast surgery

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1.0 Specific Aims

Post-operative nausea and vomiting (PONV) is a common problem that significantly impacts patient comfort and satisfaction and can delay discharge. The breast surgery population is especially at risk for PONV, given that 2 of the leading risk factors for PONV, female gender and use of peri-operative narcotics, are nearly universal. While the use of prophylactic anti-emetics significantly reduces the incidence of PONV, it still remains a significant problem, especially among high risk patients (i.e., those with a history of PONV or motion sickness). Stimulation of the acupoint Pericardium 6 (P6) has been demonstrated to be effective at both preventing and treating nausea and vomiting in multiple settings and has specifically been demonstrated to be as effective as pharmacological anti-emetics in PONV.[1] However, the role of P6 as an adjunct to multi-agent prophylaxis is less clear. P6 stimulation can be accomplished through needle insertion, acupressure, or electrical stimulation. Recently, two randomized trials in Europe and Asia have reported positive results in PONV prevention using intra-operative electrical stimulation of P6 with a neuromuscular blockade monitor (NMBM).[2, 3] The advantage to this method is that it employs a standard anesthesia tool, and, beyond anesthesiologist training on P6 point location, requires no additional resources for implementation. However, both of these trials compared NMBM to no prophylaxis rather than as an adjunct to pharmacological prophylaxis. We recently presented a small case series in which we employed intraoperative NMBM stimulation of P6 along with pharmacological prophylaxis in patients with a history of PONV (despite previous pharmacological intervention) and found that none of these patients developed PONV with the combined treatment modalities.[4]

The proposed two-arm, randomized, double-blind (patient and assessor), controlled study will determine the initial efficacy and feasibility of anesthesiologist-provided intraoperative NMBM electrical stimulation of P6 combined with prophylactic anti-emetics versus pharmacological prophylaxis alone in women at high-risk for PONV undergoing breast surgery. This study will provide preliminary evidence of efficacy to inform the design of a larger multi-institutional trial. We will also explore predictors of response to P6 stimulation including genetic polymorphisms and expectancy. The aims of the proposed study are to:

PRIMARY AIM:

1. Examine the efficacy of electrical stimulation of P6 combined with prophylactic anti-emetics versus pharmacological prophylaxis alone in preventing the incidence of PONV following breast surgery in patients at high-risk for PONV.

SECONDARY AIMS:

1. Determine the study feasibility and effects on severity of PONV of anesthesiologist-provided intraoperative NMBM electrical stimulation of P6 combined with prophylactic anti-emetics in women at high-risk for PONV undergoing breast surgery.

2. Examine the effects of intra-operative NMBM stimulation of P6 on need for rescue anti-emetics compared to the control group.

3. Examine group differences in post-operative patient satisfaction with PONV management.

4. Explore if intra-operative NMBM stimulation of P6 results in decreased PACU length-of-stay and decreased rate of unplanned hospital admission

5. Explore the associations between genetic polymorphisms in COMT, 5HT3, OPRM1, and DRD2and response to P6 stimulation.

6. Explore the associations between expectancy and response to P6 stimulation.

2.0 Background and Significance

PONV is a common occurrence following breast surgery, with incidence reported as 30-70% in the contemporary era.[5, 6] The high rate of PONV in this population is unsurprising given that the most well-validated risk score for PONV, the Apfel score, includes 4 variables (female gender, anticipated post-operative use of narcotics, history of PONV or motion sickness, and non-smoking status) two of which are nearly universal in this population.[7] Though not examined in the original risk stratification systems, there is also an association between chemotherapy-induced nausea and vomiting (CINV) and PONV[8], which becomes relevant in an era of increasing use of neoadjuvant chemotherapy. By delaying discharge from the PACU and leading to unanticipated admission following ambulatory surgery,[9] PONV is estimated to add hundreds of millions of dollars annually to the cost of post-op care in the US.[10] In addition, prevention of PONV is a major determinant of patient satisfaction.[11]

Multi-modal anti-emetic prophylaxis employing corticosteroids, serotonin antagonists, histamine antagonists and/or dopamine antagonists significantly reduces the incidence of PONV.[12] However, PONV remains a major problem for some high-risk patients, defined as having three or more of Apfel score variables who have a predicted risk of PONV of over 60% without prophylaxis.

Evidence for P6 in PONV

One promising non-pharmacological approach to the prevention of PONV is stimulation of the acupoint Pericardium 6 (P6 or alternatively called PC6). Based on large meta-analyses and systematic reviews, P6 stimulation is recommended by consensus guidelines of the Society for Ambulatory Anesthesia as a non-pharmacological approach for the prevention of PONV, given that its efficacy has been found to be similar to prophylactic antiemetics including ondansetron, metoclopramide, and prochlorperazine.[13]

Acupuncture has been used as a treatment for various GI disturbances in China for thousands of years. The acupoint P6, located over the median nerve, on the palmar aspect of the forearm, is the most frequently used and well-studied point for the prevention and treatment of nausea and vomiting. The use of P6in preventing PONV was first reported in the west by Dundee in 1986 following a trip to China.[14] In 1996, the first systematic review of acupuncture for nausea and vomiting was performed, which included 33 trials with27 favoring P6.[1] Based on this data, in 1998 the National Institutes of Health Consensus Development Panel on acupuncture concluded that there was promising data supporting the use of acupuncture in PONV and CINV.[15] A 2009 Cochrane review specifically on P6 stimulation for the prevention of PONV examined26 trials and over 3300 patients.[16] When compared to sham, P6 stimulation was found to be more effective in preventing nausea (relative risk [RR] 0.72; 95% CI 0.56–0.91). In the nine trials which compared P6 to various antiemetics, there was no reliable difference found between antiemetics and P6 stimulation for prevention of either nausea (RR 0.82; 95% CI 0.60- 1.13) or vomiting (RR 1.01; 95% CI 0.77-1.31). While in some cases, P6 stimulation could be considered as an alternative to pharmacological anti-emetics given non-inferior efficacy and superior safety profile, the effects of anti-emetics of different classes are additive and thus the standard of care for patients at moderate or high risk of PONV is multi-agent prophylaxis.[13] Lee's 2009 review included only one study where P6 stimulation was combined with pharmacological prophylaxis and the results of this trial were unclear.[16] A Pubmed search for trials published since 2008 of P6 stimulation for PONV found 5 trials which have evaluated P6 as an adjunct to pharmacological anti-emetics, with four of the five trials showing significant benefit to adding P6 stimulation to prophylactic anti-emetics. [17-21]

Despite strong evidence from almost 30 years of trials of P6 stimulation in the prevention of PONV, there does not seem to be significant penetration of this modality into clinical practice. One factor limiting adoption is likely the burden of introducing new personnel or equipment into the peri-operative and operative

spaces. There are a number of different methods employed to stimulate P6 including traditional needle-penetrating acupuncture, electro acupuncture in which an electrical stimulating device is connected to the needle, transcutaneous electrical stimulation, or acupressure, either manual or with a commercially available band. In Lee's 2009 review, there was no significant difference in the effectiveness of the various modalities though there were no head-to-head comparisons. However, while these methods may not vary in effectiveness, they do vary widely in ease and cost of implementation. Recently, there have been a series of studies which employed peripheral nerve stimulators used to monitor neuromuscular blockade in the operating room to stimulate P6 intra-operatively to prevent PONV. [2, 3, 22, 23] Monitoring of neuromuscular blockade by electrical stimulation of a peripheral nerve is standard in modern anesthesia when a neuromuscular blocking agent is used. The degree of muscle activity elicited by a peripheral nerve stimulator, usually placed on the ulnar or facial nerve, indicates the depth of neuromuscular blockade, allowing the anesthesiologist to appropriately adjust dosing and thus decrease the incidence of side effects. The advantage to using a NMBM is that this is standard equipment used by anesthesiologists and is therefore easily generalizable as it does not require bringing in additional equipment or personnel.[24] Four recent studies using NMBM at P6 in patients undergoing laparoscopy have demonstrated that this may be an effective mode of stimulating P6 to prevent PONV, including 2 RCTS of over 200 patients each. [2, 3, 22, 23] However, none of these studies examined NMBM stimulation of P6 as an adjunct to pharmacological anti-emetics.

Mechanism of P6 in nausea and vomiting

The Chinese name for P6, Neiguan, means inner gate. The traditional uses for this point include calming the spirit and harmonizing the stomach. The mechanism by which P6 stimulation exerts anti-nausea effects remains unclear. Controlled animal and human studies have demonstrated changes in gastric motility and lower esophageal sphincter relaxation with P6 stimulation.[25-27] This appears to be vagally mediated given abolishment of the effects by vagotomy in a rabbit model. [28] In healthy human volunteers, P6 stimulation has been demonstrated to increase vagal modulation as measured by heart-rate variability. This is postulated to be via a somatoautonomic reflex involving a somatic afferent pathway and vagal efferent path. Another postulated mechanism of action is via the neurotransmitters serotonin and dopamine, which are also the targets of the most effective pharmacological anti-emetics. This hypothesis is largely extrapolated from the acupuncture analgesia literature where acupuncture's effects on levels of endogenous opioids and dopaminergic and serotonergic signaling have been well-documented.[29] Recently, in a trial of P6 stimulation for CINV, serum levels of dopamine and serotonin decreased in the treatment group but not the control group.[30]

Genetics of PONV

The risk of PONV is related to both anesthesia-specific factors such as the use of inhalational anesthetics and narcotics, as well as patient-specific factors such as female gender and smoking status. Patients with a history of either PONV or motion sickness are nearly twice as likely to experience PONV, and there is also some suggestion that tendency to PONV or motion sickness may be familial, raising the potential of a genetic predisposition.[31] Over the past 5 years, there have been a number of studies conducted to identify genetic polymorphisms associated with increased risk of PONV or CINV as well as pharmacogenomic studies focused on polymorphic variations of either the targets for specific antiemetics or metabolic enzymes to probe heterogeneity of response (reviewed in Janicki et al 2014). Reflecting the multitude of pathways involved in the pathogenesis of nausea and vomiting, genetic variants of the receptor genes for serotonin, dopamine, and opioids among others have all been found to be associated with individual susceptibility to nausea and vomiting and/or response to anti-emetics.[31] Interestingly, single-nucleotide polymorphisms (SNPs) in the O-methyltransferase gene, COMT, have recently been found to be associated with response to acupuncture in aromatase-inhibitor induced arthralgias.[32] COMT is an enzyme that regulates dopamine catabolism and in animal models acupuncture has been shown to regulate dopamine release and transmission.[33, 34] COMT polymorphisms have also been demonstrated to be associated with differential risk of PONV and post-operative pain.[35]

In order to better understand predictors of response to acupuncture for nausea and vomiting, we will examine polymorphisms of candidate genes which have been associated with risk of nausea and vomiting and with overlapping biological plausibility of acupuncture's mechanism of action. Specifically, we propose to examine SNPs in COMT, the 5-HT3 receptor, the mu-opioid receptor gene (OPRM1), and the Dopamine D2

receptor (DRD2). These findings could help elucidate the heterogeneity of acupuncture treatment response and potentially allow for personalized therapeutic approaches in the future.

Expectancy

Years of psychological research have found that expectancy is an important factor viewed as a"non-specific" effect of behavioral and pharmacological therapies. In particular, response/outcome expectancy may produce important clinical changes [36]. In a systematic review, Crow et al. [37] showed that when clinicians stated positive outcome expectations as opposed to uncertain expectations, most studies found improvements in patient self-reports of anxiety, pain, and distress. A few studies have explored the association between expectancy and clinical outcomes in the context of acupuncture [38, 39]. While these studies provided preliminary evidence that greater expectancy may produce better clinical response, none used a validated instrument to measure expectancy. A recent trial using a validated acupuncture expectancy questionnaire found that expectancy of benefit had a differential effect on outcomes based on whether patients were receiving real versus sham acupuncture [32]. In a trial of acupuncture to treat aromatase-inhibitor arthralgia in breast cancer survivors, Mao et al. reported that for patients in the sham acupuncture group there was a positive association between baseline expectancy and pain reduction. In contrast, there was no association between baseline expectancy and pain reduction in the real acupuncture group. Investigating expectancy as part of the complex mind-body interactions of acustimulation will likely yield important knowledge that is both scientifically sound and clinically meaningful to patients at risk for PONV.

3.0 Research Design and Methods

We will conduct a two-arm, randomized, double-blind, controlled trial comparing pharmacological prophylaxis alone versus intraoperative NMBM stimulation of the acupoint P6 + pharmacological prophylaxis to prevent PONV in women undergoing breast surgery. P6 stimulation with an NMBM monitor will be performed by the attending anesthesiologist and will commence after induction and be removed at the end of surgery. Patients and assessors will be blinded to group assignment. The primary endpoint is the incidence of PONV. Secondary endpoints include feasibility, severity of PONV, rescue anti-emetic use, patient satisfaction, time in PACU and hospital admission rate. We will also explore predictors of response to P6 stimulation including genetic polymorphisms and expectancy. The data provided by this preliminary study will be used to design a larger multi-institutional trial.

3.1 Patient Eligibility

Inclusion criteria:

1. Adults at least 18 years of age
2. Female gender
3. History of patient reported PONV, CINV or motion sickness
4. Patients scheduled for Breast Surgery
5. Sign an informed consent indicating they are aware of the investigational nature of this study.

Exclusion criteria:

1. Patients scheduled for paravertebral block
2. Upper extremity deformity contralateral to the site of disease that could interfere with accurate point location or alter the energy pathway as defined by traditional acupuncture theory
3. Local skin infections at or near the acustimulation site
4. Pre-existing nausea and vomiting, defined as nausea or vomiting requiring pharmacological treatment greater than 3 times in the week preceding screening
5. History of CVA or other central nervous system disorder resulting in residual weakness or paresis of

extremity contralateral to the site of disease
6. Grade III or IV upper extremity peripheral neuropathy
7. Cardiac pacemakers. Patients involved in this protocol will receive electrical stimulation. For safety reasons, electrical stimulation should be avoided in patients with pacemakers
8. Metal implants to the treatment extremity. For safety reasons, use of electrical stimulation should be avoided
9. Current acknowledged use of any illicit drugs, medical marijuana (including Marinol), or evidence of alcohol abuse as defined by The American Psychiatric Association criteria [41]. This includes patients who are currently in the recovery process.
10. Pregnancy as this would alter anesthesia plan
11. Bowel obstruction
12. Surgery that would not allow access to at least one P6 site.

3.2 Participants

Over 1000 patients undergo ambulatory breast surgery each year at MD Anderson Cancer Center. Approximately 30% of these patients receive a paravertebral block and would therefore be ineligible for this study as these patients would be expected to have a lower incidence of PONV and the block could potentially interfere with acupoint stimulation mechanism of action. On initial chart review, it appears that approximately 50% of patients would meet our eligibility criteria of being high-risk based on a history of either PONV, CINV or motion sickness, which leaves approximately 350 eligible patients per year. All eligible participants will be approached. In previous acupuncture studies of other indications, our acceptance rate has been 70-80% and attrition rate 25%. However, given that this study employs a non-needle intervention and does not require a series of treatments over a protracted period of time as in our other studies, we would expect a higher acceptance rate and no attrition, though we still may have a few drop-outs between randomization and intervention. Thus, with conservative estimates of 70% acceptance and including a 5% drop-out rate, we would expect to be able to accrue the planned 176 patients in 10 months.

3.3 Treatment Plan

The experimental group will receive anesthesiologist-provided intraoperative NMBM electrical stimulation of P6 combined with prophylactic anti-emetics, while the control group will only receive prophylactic anti-emetics.

Recruitment and registration

This study will be conducted at the University of Texas MD Anderson Cancer Center (MDACC). Patients will be identified from the breast surgery schedule. An initial screen will be conducted by the research staff member via telephone or in person for history of PONV, CINV, or motion sickness. Completion screening and consent will then take place prior to surgery, and will again be conducted by the research staff. Data collection will be completed by the participant either electronically or using paper and pencil. The electronic data collection will be done via File Maker Pro which is a HIPPA and MD Anderson approved system.

Randomization

Prior to surgery and after baseline data collection, all participants will be randomized into treatment or control groups using a form of adaptive randomization called minimization[42] for a better group balance based on participant characteristics that might be related to outcome. The factors used in the minimization will include smoking status (never smoker, former smoker, current smoker), history of PONV, prior PONV (Yes/No/Unknown), history of CINV (Yes/No/Unknown), history of motion sickness (Yes/No), and anticipated duration of surgery (running median)). We will use a deterministic probability of 0.99 in the minimization algorithm given the small sample sizes. Randomization will be completed through FileMaker Pro database. Patients and PONV evaluators will be blinded to group assignments. The attending anesthesiologist will not be blinded to group assignment as they will perform the intervention but will not be involved in PONV assessment.

Acupoint stimulation procedure

Control group: Patients in the control group will have pads placed on at P6 and SJ5 on the contralateral arm

induction, however, electrical stimulation will not be given.

Treatment group: Patients in the treatment group will have pre-gelled silver electrodes placed at P6 and SJ5 on the contralateral arm at induction. P6 is located on the palmar aspect of the forearm 2 cun (1 cun is equivalent to the width of the interphalangeal of the thumb of the patient) proximal to the anterior crease of the wrist, between the tendons of the palmaris longus and flexor carpi radialis muscles. SJ5 is located on the dorsal aspect of the forearm directly opposite P6, 2 cun above the posterior crease of the wrist. This second electrode acts as a skin surface electrode to allow electrical current through the P6 acupoint.

After induction, and before incision, electrical stimulation will be initiated at 1mHz, 1 pulse/second using two leads on a nerve stimulator (Neurotech, LLC, Elmgrove, WI). Stimulation will be continued throughout the surgery and discontinued at the time of extubation. Any residual gel from the electrodes will be removed.

Anesthetic management
After obtaining informed consent, and establishment of IV access, patients will receive premedications in the holding area, consisting of Pepcid 20mg IV, Versed 1-2mg IV, and Fentanyl 25-50mcgm IV. In the OR, standard ASA monitors will be placed and the patient will be pre-oxygenated. Induction via Propofol IV1-2.5 mg/kg is followed by laryngeal mask placement. If endotracheal tube placement is indicated, neuromuscular blocking agent will be given IV, either Rocuronium 0.3-1.2 mg/kg or Succinylcholine 0.5-1.5 mg/kg. Anesthesia maintenance will be with inhalational agent of Sevoflurane or Desflurane. IV Fentanyl or Dilaudid will be titrated in accordance with the patient's individual physiological response to the surgical stimulation. Decadron 10 mg IV x1 will be given intraoperatively and Zofran 4 mg IV x1 and Phenergan 6.25 mg IV x 1 will be given at closing. The airway will be extubated in accordance with standard guidelines of care, and the patient will be brought to the PACU.

Antiemetics
All patients will receive standard prophylactic antiemetics consisting of Zofran 4 mg IV x1, Dexamethasone 10 mg IV x 1, Phenergan 6.25 mg IV x 1, and Pepcid 10mg x 1 intraoperatively as noted above. Rescue treatment for PONV will be according to our standard post-operative algorithm, i.e. for PONV occurring less than 4 hours following PACU arrival: Granisetron 1 mg IV x 1. If ineffective, this can be followed by Promethazine 6.25 mg IV up to 2 doses, after which the PACU attending is called for further intervention. For PONV occurring greater 4 hours following PACU arrival, Ondansetron 4 mg IV can be given for two doses.

Assessment
Assessment of PONV and Pain will be conducted by the PACU nurse or research member. Per PACU procedures, the nurse will also determine when the patient is ready for PACU discharge. This nurse or research member will be blinded to group assignment.

Anesthesiologist training
P6 NBMN stimulation will be performed by a team of 4 MDACC anesthesiology faculty members. Each member has experience in using NMBM stimulation. Each participant will have training in P6 and SJ5 acupoint location with a licensed acupuncturist (KG or JM) and will be observed placing NMBM monitor on appropriate acupoints.

3.4 Pretreatment evaluation: Prior to beginning treatment, the following will be provided/obtained:

a. Review of the nature and purpose of the study with potential subjects and verification that the patient meets all eligibility criteria.
b. Written informed consent from patients who agree to participate in the study prior to any study procedures.

c. Complete history and physical examination of eligible subjects.

d. Review and documentation on the worksheet of specific medical history information including type of malignancy and previous surgical history.
e. Documentation of all medications taken by the patient in the preceding 30 days.
f. Review of the patient's available medical record to ensure that inclusion and exclusion criteria have been met.
g. Smoking status as stated in electronic medical record.
h. Acupuncture Expectancy Scale (AES). This 4-item instrument will be administered at time of consent.

3.5 Measurement of effects:

1. PONV: Nausea and vomiting will be assessed at baseline (regain of consciousness as defined by ability to answer questions regarding presence or absence of nausea and pain), every 15 minutes until discharged from PACU. Nausea will be assessed verbally on an eleven-point scale (0=no nausea to 10=worst nausea imaginable). Vomiting is defined as the forceful expulsion of gastric contents from the mouth. Retching, i.e. an active attempt to vomit without expulsion of gastric contents, will be categorized as vomiting. Complete control will be defined as no nausea ≥3, vomiting, or use of anti-emetics during PACU stay. Incidence of nausea, intensity of nausea, incidence of vomiting, and number of vomiting episodes will also be measured.
2. Feasibility as defined by at least 20% of screened patients meeting inclusion criteria ability, 50% of these patients consenting, and 75% of patients within the acupuncture study arm completing all procedures.
3. Use of rescue anti-emetics. Use of rescue antiemetics will be as per PACU protocol and will be abstracted from the electronic medical record.
4. Patient satisfaction. Patients will be asked to rate their satisfaction with PONV management at time of discharge from PACU (0= very dissatisfied to 10= most satisfied imaginable).
5. Pain. Pain will be assessed every 15 minutes verbally on an eleven-point scale (0=no pain to 10=worst pain imaginable).
6. Postoperative analgesic use. Total MEDD of postoperative analgesia will be abstracted from the electronic medical record.
7. Total time in PACU will be calculated from medical record.
8. Need and basis for hospital admission will be abstracted from the medical record.
9. A maximum of 10 cubic centimeters of whole blood will be collected intra-operatively in an anti-coagulant treated tube and stored at -80°C until ready for processing to explore the associations between genetic polymorphisms in COMT, 5HT3, OPRM1, and DRD2 and response to P6 stimulation.

3.6 Evaluation of Toxicity
Nurses or research members will evaluate for symptoms of muscle fatigue, numbness, tingling, or pain of stimulated extremity. Prolonged nerve stimulation could theoretically result in tetanic muscle contraction and nerve damage, though this has not been reported in the literature. Rare contact dermatitis has been reported to electrode gel. Adverse events will be captured. The symptoms assessed using the Evaluation of Toxicity will be considered an adverse event if graded 4 or above on a 0 to 10 scale.

3.7 Criteria for Removal from the Study
Subjects will be removed from the study if any of the following occur:

a. Patient request for removal.
b. Primary physician request for removal.
c. Surgical complication such as infection, bleeding, organ failure, or mechanical bowel obstruction.
d. Development of skin changes at the acustimulation sites during the period of treatment.

3.8 Statistical considerations:

Analysis Methods:

The primary aim of this study is to examine the efficacy of electrical stimulation of P6 combined with prophylacticanti-emetics versus pharmacological prophylaxis alone in preventing the incidence PONV following breast surgery in patients at high-risk for PONV. We will make a preliminary evaluation of efficacy by testing for a difference in incidence of PONV between study arms. If a subject fails to have complete control of nausea (as defined in Section 3.5) at any time during her PACU stay, she will be considered as having PONV. We will use a 1-sided chi-squared test of proportions with Type I error of 0.1 to test for difference in PONV incidence.

Secondary endpoints of interest are feasibility of the study, use of rescue anti-emetic medications, post-operative patient satisfaction, PACU length-of-stay, hospital admission, and patient expectations. We will calculate rates, frequencies, and 90% confidence intervals (CIs), as applicable, and will judge thistrial feasible if at least 20% of screened patients meet inclusion criteria, 50% of patients who meet the inclusion criteria consent, and 75% of patients within the acupuncture arm complete all procedures. We will also calculate the appropriate summary statistics and 90% CIs for other secondary endpoints by group, as well as for differences between groups. We will evaluate preliminary differences in the severity of PONV and use of rescue anti-emetic medications between groups using mixed model analyses. Additionally, we will explore associations between genetic polymorphisms in COMT, 5HT3, OPRM1, and DRD2 and response to P6 stimulation using ANOVA models with factors such as the number of matching alleles and treatment group. Finally, we will tabulate and compare adverse events by study arm.

Sample size calculations:
This study is powered for a preliminary examination of efficacy in order to determine whether there is early evidence of efficacy to justify moving forward with further studies of intra-operative NMBM stimulation of P6 to prevent PONV. Similar studies in other patient populations in which pharmacological prophylaxis was used with or without acupoint stimulation found that incidence of PONV was approximately 0.4 in the control group and 0.25 in the experimental group.[17-20] To test whether a similar difference exists in this patient population, we will need 88 patients per arm to achieve 80% power when using a 1-sided chi-squared test with $\alpha = 0.1$.
With regard to the secondary objective of feasibility evaluation, to achieve a sample size of 88 perarm, assuming 20% of screened patients meet the inclusion criteria and of those patients, 50% consent, we would need to screen 1,760 potential subjects to obtain 352 eligible subjects, and of these, 176 would consent to be in the study. Under these circumstances, the half-width for a 90% confidence interval regarding inclusion criteria would be 0.016 and the half-width for a 90% confidence interval regarding consent would be 0.044. If 75% of the subjects within the acupuncture arm complete the study, the 90% confidence interval around this statistic would be 0.076 with N=88 for the acupuncture arm.

Missing Data:
Given a patient's active involvement only lasts until discharge from PACU, we do not expect to have issues with missing data and drop-outs, and our primary analyses will be based on observed data. Should we find that missing data and/or drop-outs become an issue (> 10% in either arm), we will conduct additional sensitivity analyses using approaches including multiple imputation, pattern-mixture models, and selection models to account for potential missing-at-random or missing-not-at-random mechanisms.[43] The primary along with the sensitivity analyses will provide a comprehensive assessment of the effects of interest, and similar results based on these analyses would strengthen our preliminary study findings.

Interim Analysis:
No formal interim analyses are planned, however, we will present aggregate efficacy and safety data to the MDACC DSMB so that they can assess whether enrollment should halt for futility or toxicity reasons. In addition to summary statistics, we will also calculate $\Pr[\pi_{IES} < \pi_{SOC} \mid \text{data}]$, where π_{IES} and π_{SOC} are the proportions of women who report complete control of nausea (as defined in Section 3.5 of the protocol) at any time during the PACU stay in the electrical stimulation arm and control arm, respectively. This probability will

also be presented in the DSMB report to assess whether enrollment should continue in the trial. When calculating this probability, we will assume that both π_{IES} and π_{SOC} have a prior beta distribution with alpha = 0.8 and beta = 1.2. In addition, we will examine the defined feasibility criteria during the annual DSMB report. If the results look sufficiently clear that feasibility is not achieved, we will consider terminating the study, provided that the DSMB recommends so.

3.9 Treatment of Data

Support for data analysis will be provided by an experienced statistician. All data will be entered initially entered by hand onto forms or electronically by the attending nurse, research member, or obtained from the patient record (vitals and laboratory tests). The data will be checked for standard nomenclatureand completeness during the patient's stay and entered into a password protected database created in FileMaker Pro.

The patient's will be identified only by assigned sequential ID number (obtained from the randomization list) to insure both patient confidentiality and to provide a key to the patient information in the patient's record. The key will be kept in a separate file and not with the datafile.

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