Open-Label Randomized Controlled Trial to Assess Preoperative Acupuncture for Patients Undergoing Total Knee or Hip Arthroplasty

OVERVIEW

Acupuncture has been extensively practiced and studied worldwide, particularly as a part of Eastern medicine, but it is a relatively uncommon therapy offered in Western medical institutions, such as those in the United States. Considering the commonly cited benefits of acupuncture, such as reduced anxiety and pain, hospitals throughout the United States have the opportunity to implement acupuncture as a cost-effective and safe technique for improving surgical outcomes.

Acupuncture administered in the preoperative period can be particularly effective for reducing preoperative anxiety, postoperative pain, postoperative opioid consumption, and postoperative nausea and vomiting. Consequently, preoperative acupuncture can improve patient satisfaction and decrease hospital costs. However, due to lack of implementation and experience, further research is needed to establish the safety and efficacy of preoperative acupuncture in the United States medical practices.

At the Bone-and-Joint Institute at Hartford Hospital, where this study is proposed, a quality study on total knee or hip arthroplasty patients found that 21% of its monthly patients were “high-anxiety” according to the Amsterdam Preoperative Anxiety and Information Scale (APAIS). Thus, there is a significant population of patients that would benefit from a procedure to reduce preoperative anxiety at our facility.

This proposal is for a prospective, open-label, randomized controlled trial to determine the effect of preoperative acupuncture on preoperative anxiety and postoperative pain for high-anxiety patients undergoing total hip arthroplasty or total knee arthroplasty. We hypothesize that preoperative acupuncture will reduce preoperative anxiety and postoperative pain as well as reduce postoperative nausea and vomiting and opioid consumption and improve patient satisfaction. The study population is to include adult patients undergoing lower extremity total joint arthroplasty, including of the hip and knee joints, at the Bone-and-Joint Institute at Hartford Hospital.

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1.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objectives: In patients with high anxiety undergoing THA or TKA:

1) Determine if preoperative acupuncture reduces preoperative anxiety in the acupuncture group.

2) Examine postoperative pain following acupuncture compared to control.

Secondary Objective: To determine the safety of preoperative acupuncture by recording complications throughout hospital length of stay; to determine whether preoperative acupuncture reduces postoperative nausea and vomiting, reduces postoperative opioid consumption, reduces anxiolytics need during hospitalization and improves satisfaction compared to control in high-anxiety patients undergoing THA or TKA.

2.0 BACKGROUND AND RATIONALE

Acupuncture has been a practice of Chinese medicine for over 2,500 years for treating diseases, relieving pain, and more recently for improving the outcomes of surgery.[1] In the United States, however, acupuncture was relatively unheard of as a medical practice until the 1970s, and the nation has since remained hesitant to implement it in the hospital.[2] As a result, while the research on acupuncture shows potential benefits for both patients and providers, most of these studies have been conducted outside of the United States, which likely has contributed to the nation's cautious stance. Practitioners and researchers, therefore, need to demonstrate and determine whether the touted benefits of acupuncture can be extended to practices in the United States.

Postoperative pain is commonly studied as a primary outcome of acupuncture treatment, and improvements in pain are often cited as a benefit.[3-11] For example, in a large study that aimed to evaluate an acupuncture rehabilitation program on 2,282 patients who underwent total knee arthroplasty (TKA) or total hip arthroplasty (THA), patients on average reported a 45% reduction in pain following acupuncture treatment.[3] Another study randomized 80 patients who received TKA to receive either postoperative acupuncture treatment or standard rehabilitation care, and results showed that patients in the acupuncture group experienced significantly reduced postoperative pain, increased knee range-of-motion, and faster rehabilitation time.[7] Heightened postoperative pain is, understandably, a strong predictor of worsened surgical outcomes and patient dissatisfaction, and, according to a systematic review of nearly 30,000 TKA patients, the most consistent predictor of postoperative pain is preoperative pain.[12] Therefore, perhaps the best method for improving surgical outcomes and patient satisfaction is to target both postoperative and preoperative pain. Since few studies have explored the analgesic effects of acupuncture in the preoperative period, there is an opportunity for future research to determine whether the pain-reducing effects of acupuncture can be used in the preoperative period to improve surgical outcomes and patient satisfaction.

Intra- and postoperative opioid consumption is another commonly studied outcome of acupuncture.[13] In a randomized controlled trial (RCT) of 54 patients receiving THA, researchers randomized patients to receive either auricular (of the ear) or sham acupuncture treatment and compared the amount of piritramide (a synthetic opioid closely related to fentanyl and commonly used in European countries) used

intraoperatively.[9] The results showed that patients in the acupuncture group required significantly less piritramide intraoperatively compared with sham (37 ± 18 mg vs. 54 ± 21 mg). A similarly constructed RCT also studied the effects of preoperative auricular acupuncture on intraoperative opioid use, but researchers instead studied fentanyl use and included patients undergoing TKA.[14] These researchers, too, found that patients in the acupuncture group required significantly less opioid during surgery than patients in the sham acupuncture group (620.7 ± 258.2 μg vs. 868.6 ± 319.3 μg). Further, these patients on average lasted longer before requesting analgesia and exhibited lower visual pain scores. Several other studies have also demonstrated that preoperative acupuncture lessens the need for opioids during and after surgery.[4,10,15,16] Reducing opioid consumption through the introduction of safely administered acupuncture poses a potential net improvement for patient safety and hospital costs.

Perhaps the most commonly cited benefit of acupuncture is increased relaxation and decreased anxiety, and several systematic reviews have reported that these benefits persist in the clinic.[1,3,17] For patients with anxiety, depression, or other mental ailments, this is an important finding considering the substantial evidence linking poor mental health with significantly worse surgical outcomes.[18-27] For example, one systematic review that accounted for 53,562 patients undergoing THA concluded that depression and anxiety were associated with increased postoperative pain, and another that accounted for 95,560 patients undergoing TKA found that the most consistent and significant indicator of dissatisfaction related to surgery was preoperative anxiety.[27,28] Despite this evidence that poor preoperative mental health is detrimental to both practitioners and patients of surgery, there are currently no guidelines for improving preoperative mental health conditions.[25]

Preoperative acupuncture can serve as an ideal therapy to safely reduce preoperative anxiety and improve surgical outcomes. It has been repeatedly demonstrated as a safe, cost-effective, and time-effective procedure for reducing preoperative anxiety, postoperative pain, total opioid consumption, and postoperative nausea and vomiting while increasing patient satisfaction.[4,13,29] However, medical practices in the United States have largely forgone the potential upsides of acupuncture due to minimal existing research undertaken within the country. Therefore, there is an opportunity for United States medical researchers and practitioners to demonstrate the potential for preoperative acupuncture as a safe and effective therapy to improve surgical outcomes for both patients and providers.

This proposal suggests a robust study to evaluate the safety and efficacy of preoperative acupuncture performed on high-anxiety patients undergoing THA or TKA at the Bone-and-Joint Institute (BJI) at Hartford Hospital. Evidence suggests that the outcomes of THA and TKA in particular are associated with preoperative anxiety and postoperative pain.[30] Patients will be classified as high-anxiety based on having an APAIS-A-T (Appendix I) score greater than 10, a threshold used in previous studies.[31-34]

3.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

3.1 Design

This is a prospective, open-label, randomized controlled trial to determine the efficacy and safety of preoperative acupuncture on high-anxiety patients undergoing TKA or THA. Patients scheduled for THA or TKA to be performed by one of the IRB approved orthopedic surgeons at the BJI will be screened for high preoperative anxiety one week prior to procedure in the PREPARE Center, the BJI's preoperative services clinic, using printed copies of the APAIS questionnaire. The APAIS will be used as a screening tool and is considered optional for the patient to complete and not a standard of care measure. High-anxiety patients consenting to the study will be randomized to receive either 1) preoperative acupuncture (Acupuncture) or 2) no intervention (Control). Results from a quality study at the PREPARE clinic demonstrates that number of patients with high-anxiety entering the clinic is 30 per month. Accounting for the availability of investigators and surgeons, the study period is estimated to last approximately two years to obtain the 50 patients, 25 per group that we aim to enroll in this study. There will be an interim analysis after enrolling 14-15 patients in each group (60%) to re-estimate the sample size using more appropriate data (see sample size estimate section). Each patient will be enrolled in the study from the time of consent and will be followed up to 30 days postoperatively. Investigators performing the acupuncture will be licensed and certified throughout the study duration.

3.2 Randomization

Patients will be randomized immediately following the consenting process. Randomization will be achieved using a random number generator, which will randomly produce a 0, representing the Acupuncture group, or a 1, representing the Control group, for each patient. Patients will immediately be informed, for their convenience, of their group assignment given the non-blinded nature of the trial.

3.3 Acupuncture Intervention

Prior to acupuncture treatment, all patients in the acupuncture group will receive a medical assessment including a review of the patient's medical chart. The acupuncture intervention will include a combination of auricular and body acupuncture. The auricular points used will include: Shen men, Zero point, Tranquilizer point and Master cerebral. The body point will be the wrist acupuncture point PC6. All points will be bilateral. With the patient seated, body and auricular points will be wiped with 70% isopropyl alcohol wipes. After about 1 minute of drying, the acupuncture needles will be inserted. The needles used on both ear and wrist points will be the DBC Detox-5 needles. They will be retained for approximately 20 minutes, removed and placed into a sharps container.

3.4 Therapy Materials

- Alcohol wipes
  - Disposable, individually sealed alcohol prep pads
  - Each pad is saturated with 70% isopropyl alcohol
  - 1” x 2.5”
- Acupuncture needles
  - 1) SEIRIN J-Type Acupuncture Needles (SKU: SJ.18X30; Figure 1)
    - Length: 30 mm
    - Diameter: 0.18 mm
  - 2) SEIRIN J-Type Acupuncture Needles (SKU: SJ.20X30)
    - Length: 30 mm
    - Diameter: 0.20 mm
  - 3) DBC™ Detox-5 Acupuncture Needles(SKU: DTX.20X13; Figure 2)
    - Length: 13 mm
    - Diameter: 0.20 mm

Figure 1. Seirin needles (SEIRIN® (SKU: SJ.18X30)

Figure 2. DBC™ Detox-5 Acupuncture Needles (SKU: DTX.20X13).

4.0 CRITERIA FOR SUBJECT ELIGIBILITY

4.1. Subject Inclusion Criteria

- Female or male patients undergoing TKA or THA surgery at the Bone-and-Joint Institute at Hartford Hospital
- High-anxiety (APAIS-A-T >10)
- Age: 52 to 85

4.2. Subject Exclusion Criteria

- Unable to give consent
- Uncontrolled diabetes (HbA1c ≥ 8.0%)
- Infection at any of the acupuncture points
- Known allergy to metals
- Abnormal laboratory blood work values (INR>1.5, if available; platelet count <70,000, if available)
- Patients with active ongoing coagulopathy based on lab data (INR >1.5) and/or on current anticoagulant use which increases bleeding risk.
- Women in reproductive age or under the age of 52 years old, as acupuncture is not recommended with pregnancy
- Non-English speaking
- Revision TKA or THA

5.0 RECRUITMENT PLAN

Potential patients who are scheduled for either TKA or THA will receive the APAIS questionnaire form with the other preoperative forms that they are typically receiving through Force Therapeutic platform 30 days prior to their scheduled surgery date. A

member of the study personnel will receive the completed APAIS and will screen potential subjects for the other eligibility criteria using our electronic medical record (EMR) system (EPIC). The study personnel will notify PREPARE providers of high-anxiety patients a day prior to their PREPARE visit to plan to keep those patients in a separate room for consenting. A member of the study personnel will meet with the potential subjects for consenting after they complete their visit with the provider. During the consenting process, patients will be informed of the study details, benefits, risks, and enrollment process and will be given necessary time for questions and concerns. Specifically, patients will be made aware that this is a randomized trial and that they will, therefore, be randomized to one of two study groups. Patients providing consent will be enrolled in the study.

If the consenting process cannot be conducted in-person, the same discussion of consent will be conducted via video call or by telephone, following the Hartford Healthcare (HHC) consenting guidelines, and the link to the electronic consent form will be sent via email using an HHC-licensed Research Electronic Database Capture (REDCap) database.

For enrolled patients, two signed consent forms will be printed, of which one will be stored in a patient binder, and the other will be given to the patient on the day of surgery. Documentation of the consenting process and the printed consent form will be scanned and uploaded to EPIC. Enrolled patients will be registered into a study-specific REDCap database and given a unique study ID number along with their randomly assigned study group. A linkage file will be created connecting the patient study IDs to their corresponding medical record numbers (MRNs), and this file will be stored on a secured, password-protected HHC server.

6.0 PRETREATMENT EVALUATION

Baseline preoperative history and physical exam evaluations from the PREPARE clinic of the Bone-and-Joint Institute will be used to collect the clinical demographic variables listed below. Laboratory tests, shown below, are also recommended, and corresponding results will be gathered if they occurred within 60 days prior to surgery.

<u>Clinical Demographic Variables of Interest</u>

- Age
- Gender
- Race and ethnicity
- BMI
- History of bleeding disorders
- History of coagulopathy
- History of acupuncture treatment
- Uncontrolled diabetes mellitus
- Present infection at the sites of acupuncture
- History of mental illness
- History of TKA or THA surgery
- Known allergy to metal

- INR (if available)
- Platelet count (if available)

7.0 INTERVENTION ORDER OF EVENTS

7.1 Acupuncture Group

1. On the day of surgery and prior to procedure, study patients will be waiting in the preoperative area.
2. The patient will be placed in bay #1 or other bay if #1 is not available in the preoperative area.
3. A member of the study personnel will assess the patient's baseline anxiety and pain.
4. The assigned acupuncturist will conduct a preoperative medical assessment and chart review on the patient prior to intervention.
5. The patient will then undergo the acupuncture procedure given by the assigned acupuncturist.
6. Anxiety and pain will be reassessed by a member of the study personnel after the procedure.
7. The patient will undergo their surgical procedure.
8. The patient will be reevaluated for pain three times; when they arrive to the post-anesthesia recovery unit (PACU), after an hour, and after 3 hours.
9. The patient will be reevaluated for PONV/Impact score two times; after an hour from their arrival to the post-anesthesia recovery unit (PACU), and after 3 hours. Postoperative antiemetics used will also be collected from the patient's chart retrospectively, following enrollment.
10. Postoperative opioid consumption and anxiolytics used throughout hospitalization will be collected from the patient's chart retrospectively, following enrollment.
11. Admission and discharge dates & times will be collected directly from the patient's chart retrospectively, following enrollment and used to determine total hospital length of stay.
12. Patient satisfaction regarding surgery will be evaluated within a week after the discharge from the hospital.

7.2 Control Group

1. On the day of surgery and prior to procedure, study patients will be waiting in the preoperative area.
2. The patient will be placed in bay #1 or other bay if #1 is not available in the preoperative area.
3. A member of the study personnel will assess the patient's baseline anxiety and pain.
4. The patient will undergo their surgical procedure.
5. The patient will be reevaluated for pain three times; when they arrive to the post-anesthesia recovery unit (PACU), after an hour, and after three hours.
6. The patient will be reevaluated for PONV/Impact score two times; after an hour from their arrival to the post-anesthesia recovery unit (PACU), and after 3 hours. Postoperative antiemetics used will also be collected from

the patient's chart retrospectively, following enrollment.

7. Postoperative opioid consumption and anxiolytics used throughout hospitalization will be collected from the patient's chart retrospectively, following enrollment.
8. Admission and discharge dates & times will be collected directly from the patient's chart retrospectively, following enrollment and used to determine total hospital length of stay.
9. Patient satisfaction regarding surgery will be evaluated within a week after the discharge from the hospital.

8.0 OUTCOME EVALUATION

All outcomes will be measured during the time periods illustrated in Table 1 using the following measurement methods:

- PreOP anxiety: Amsterdam Preoperative Anxiety and Information Scale (APAIS; Appendix I)
- State anxiety: Visual Analogue Score (VAS; Appendix VI) will be compared between pre and post acupuncture in the same patient within the acupuncture group.
- State anxiety: Visual Analogue Score (VAS; Appendix VI) preop anxiety assessment will be compared between the two groups to assess their baseline preop anxiety status on day of surgery.
- Pain: 11-point Numeric Pain Rating Scale (NPS; Appendix V) will be compared between the two groups
- Postoperative opioid consumption: collected through EPIC and converted into morphine milligram equivalents (MMEs) using Appendix IV. This will be compared between the two groups.Postoperative nausea and vomiting (PONV): PONV impact score (Appendix VII) will be compared between the two groups. Additionally, postoperative antiemetics needed during hospital admission will be collected directly from EPIC and compared between the two groups.
- Satisfaction with surgery: questionnaire (Appendix III) provided by a member of the study personnel by phone within a week after the discharge from the hospital.
- Adverse events related to the interventions will be recordedthroughout enrollment.
- Anxiolytics medication needed throughout hospitalization will be collected directly from EPIC and compared between the two groups.
- Hospital length of stay will be collected directly from EPIC using hospital admission and discharge dates & times; this will be compared between the two groups.

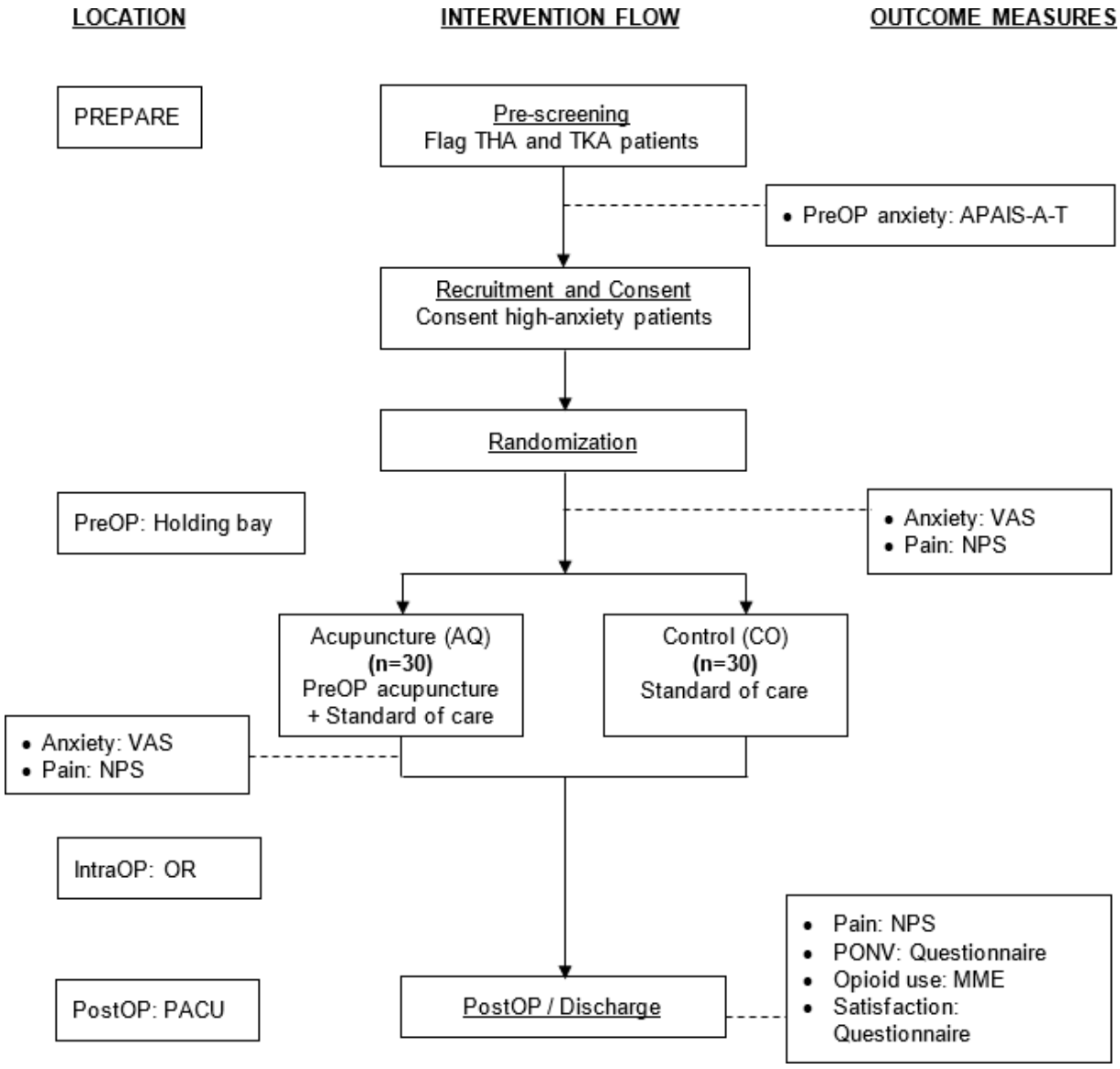
Table 1. Outcome measurement time, researcher-to-patient interface, and method for all study outcomes.

Time	Interface	Outcome/ Measurement (Acupuncture)	Outcome/ Measurement (Control)
-10 to -7 days	PREPARE Center	• Preoperative anxiety/APAIS	• Preoperative anxiety/APAIS

PreAQ/PreOP	Holding bay	• Anxiety/VAS • Pain/NPS • Anxiolytics	• Anxiety/VAS • Pain/VAS • Anxiolytics
PostAQ/PreOP	Holding bay	• Anxiety/VAS • Pain/NPS	NA
PostOP	PACU: on arrival, 1 hour, and 3 hours	• Pain/NPS • Anxiolytics	• Pain/NPS • Anxiolytics
PostOP	PACU: 1 hour, and 3 hours after arrival	• PONV/impact score	• PONV/impact score
PO-Discharge	chart review	• Opioid use/MME • Anxiolytics • Antiemetics • Hospital length of stay	• Opioid use/MME • Anxiolytics • Antiemetics • Hospital length of stay
Within a week from discharge	Phone call	• Satisfaction questionnaires	• Satisfaction questionnaires

Abbreviations: NPS, numeric pain rating scale; PACU, post-anesthesia care unit; PONV, postoperative nausea and vomiting; POD, postoperative day.

Figure 3. Protocol schema.



9.0 DATA MANAGEMENT

A Clinical Research Coordinator (CRC) will be assigned to the study. The responsibilities of the CRC will include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the protocol study team.

The data collected for this study will be entered into a database in an HHC-licensed version of REDCap. Source documentation will be available to support the computerized patient record and will be stored at the clinical anesthesia research office in a double-locked environment. All efforts will be made to ensure maintenance of patient confidentiality and HIPAA compliance. All data will be maintained on the REDCap database which will be stored on a secure HHC server and access will be protected by password. This database will only be accessible to the trained study personnel.

9.1 Quality Assurance

Monthly meetings will be conducted to monitor patient accruals and quality of data. Potential problems will be brought to the attention of the entire study team during the monthly meeting for discussion, action, and resolution.

At *approximately* 55-60% enrollment (14-15 per group depending on enrollment pace) point of the study, the research team will assess the accrued results in a planned interim analysis to determine whether any changes are necessary.

9.2 Data and Safety Monitoring

The study investigators will be responsible for the safety of the study participants, and they will stress the importance of reporting adverse events to the participants. Investigators will also consistently monitor each participant for adverse events. Adverse events, related or unrelated to the acupuncture procedure, will be reported, attributed, and graded for severity by the clinician and documented in EPIC. Serious adverse events or unanticipated problems will be reported to the IRB.

10.0 PROTECTION OF HUMAN SUBJECTS

Every effort will be made to ensure the safety of our patients and the confidentiality of their medical information. During the enrollment and consent process, all risks, benefits, side effects, and alternatives will be discussed. Also, it will be stressed that this is a voluntary study and that the patient can withdraw without prejudice at any time.

Benefits

The potential benefit of this study is that preoperative acupuncture is effective in reducing preoperative anxiety and postoperative pain in patients undergoing lower extremity total joint arthroplasty. Such a reduction in postoperative pain and anxiety could potentially increase overall patient satisfaction. Further, patients will not be compensated for participating in this study, but they will receive the acupuncture service at no cost.

Risks

The risks of participation include the risks associated with performing acupuncture include, but are not limited to, the following: minor bleeding, pain, pneumothorax, abdominal injuries, heart injuries, CNS injuries, neck injuries, eye injuries, peripheral nerve injuries, and infection.

Alternatives

The alternative to acupuncture for addressing high-anxiety patients is the standard of care. For pain, this includes the use of standard pain medications, including opioid and non-opioid analgesics, in addition to regional blocks. For anxiety, this includes the regular use of anxiolytic medications and psychological consultation referrals. These standard-of-care procedures will not be replaced by acupuncture and rather performed in adjunct. A patient's decision on whether or not to participate in this study will not affect the availability of standard and supportive measures.

Costs

There will be no additional cost incurred by the participant to participate in the study.

Acupuncture materials and service will be provided at no additional cost to the patients enrolled in the study and will be provided by one of the study investigators.

Voluntary Nature of Study

Participation in this study is entirely voluntary. Patients will be informed of the extent of the risks, benefits, adverse events, alternatives/options for treatment, financial costs/burdens, and the voluntary nature of the study. The responsible investigator will ensure that this study is conducted in agreement with the Declaration of Helsinki (Tokyo, Venice, Hong Kong, Somerset West, and Edinburgh amendments). The study will seek in every way to protect the rights of human subjects. No patient will be required to participate in the study, and participation or lack of participation will not affect the patient's subsequent care or treatment.

Participation will be entirely voluntary and subjects will not be reimbursed for participation in the study. Throughout the study, patient confidentiality will be maintained. No results of the study will be presented or discussed in a fashion that will allow identification of a particular patient in the study. All adverse events will be fully disclosed to the IRB in a timely fashion as required.

10.1 Privacy

HHC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and HRPP (IRB/HRPP).

10.2 Adverse Events

The incidence and severity of adverse events is highly dependent on the experience and skill of the practitioner, and when provided by a physician, acupuncture is accepted as a safe treatment.[29,36,37] Acupuncture-related adverse events occur in about 6% of cases; the vast majority of these are usually minor and most commonly include bleeding, discomfort, and residual pain at the insertion points.[36] Serious acupuncture-related adverse events occur in just 0.024% of cases.[37] Of these, the most frequently cited include: pneumothorax, abdominal injuries, heart injuries, CNS injuries, neck injuries, eye injuries, peripheral nerve injuries, and infection.[37] Though acupuncture-related deaths have been reported, the incidence is statistically negligible, and even surveys covering more than 3 million acupuncture treatments report no cases of death.[38]

Adverse events will be monitored during and after acupuncture and throughout admission. Events will be recorded as safety measures. Emergency visits and hospital readmissions stated in EPIC will be recorded up to thirty days postoperatively.

10.3 Serious Adverse Event (SAE) Reporting

The risks associated with acupuncture are viewed as minimal risk. Although we have assessed the proposed study as one of minimal risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk of this procedure in this context. Therefore, we provide a plan for monitoring the safety of the participants in the study as

follows:

Attribution of Adverse Events

Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator according to the following categories:

- Definite: Adverse event is clearly related to investigational procedures(s)/agent(s)
- Probable: Adverse event is likely related to investigational procedures(s)/agent(s)
- Possible: Adverse event may be related to investigational procedures(s)/agent(s)
- Unlikely: Adverse event is likely not to be related to the investigational procedures(s)/agent(s)
- Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s)

Grading Adverse Events

The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event
2. Moderate adverse event
3. Severe adverse event

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in thisdefinition

Note: hospital admission for a planned procedure/disease treatment is not considered an SAE. Additionally, grade 1-3 events from the following list of protocol complications will be considered expected on study and not reportable as SAEs: bleeding, discomfort, and residual pain at the insertion points. These will be tracked separately through the protocol data collection sheets.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30 days after the participant's last investigational treatment or intervention. If an SAE requires submission to the IRB office per IRB SOP, the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires submitting the SAE electronically using iRIS. A copy of the SAE report should be retained in the patient's study chart for auditing purposes. The report should contain the following information: subject's initials, medical record number, protocol number, and title. The

PI's signature and the date it was signed are required on the completed report.

Data to be entered for SAEs:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
- An explanation of how the AE was handled
- A description of the subject's condition
- Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consentform
- If the SAE is an Unanticipated Problem

Reporting Adverse Events to Investigators

For the current study, all investigators listed on the protocol will be notified, and the principal investigator will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

11.0 STATISTICAL ANALYSES

Sample Size

There was only one study[14] that provided appropriate data for a power analysis for the primary outcome, pain, and one study that provided appropriate data for the primary outcome, anxiety[39]. The sample size requirements based on the results from each of the studies are displayed in the following tables. Since our time points differ from these two studies, we have chosen to perform an interim analysis after approximately 55-60% (14-15 per group depending on enrollment pace) of patients have been enrolled in order to re-estimate the required sample size. Our current sample size enrollment (50 patients) is simply based on what the study team considers the maximum number of patients that can be feasibly enrolled within the anticipated study enrollment time-frame. As shown, this number of patients (50) are more than double that of the estimated sample size needed (22) at 90% power, while accounting for 10% attrition.

Primary Outcomes: Pain
Study: Chen et al. 2015

	Measurement Method: VAS (made relative to 0-10 scale)	Total *N* Needed @ 0.80 power	Total *N* needed accounting for 10% attrition	Total *N* Needed @ 0.90 power	Total *N* needed accounting for 10% attrition

Post-Op Time	Group difference (mean±SD)				
2 hr	1.4±0.9	16	18	20	22
4 hr	1.2±0.4	8	10	8	10
8 hr	0.8±0.1	4	6	4	6
12 hr	1.0±0.2	6	8	6	8
24 hr	0.8±0.1	4	6	4	6

Primary Outcomes: Anxiety
Study: Karst et al. 2006 (treatment vs no treatment)

Measurement Method (time change)	Group Mean difference of change score	*N* Needed @ 0.80 power	*N* needed accounting for 10% attrition	*N* Needed @ 0.90 power	*N* needed accounting for 10% attrition
STAI (Baseline post-treatment)	2.83±0.72	6	8	6	8
VAS (Baseline to post-treatment)	1.44±0.34	6	8	6	8

An interim analysis was performed using data for the primary outcomes, *pain* and *anxiety*. Of note, this interim analysis was performed to re-estimate the sample size since the initial sample size estimate was based on a study with different time points than this study. Therefore, the sole purpose of this interim analysis was to re-estimate the sample size, and was not to test the hypothesis.

For the primary aim *pain*, based on data from the first 31 patients enrolled, our sample size calculation indicates that a minimum of 26 subjects per group are needed using a repeated measures design (each subject is measured 4 times) with 2 groups for a total of 52 subjects. This design achieves 81% power to test factor B1 if a Geisser-Greenhouse Corrected F Test is used with a 5% significance level and the actual effect standard deviation is 0.255 (an effect size of 0.40319). We estimate an attrition rate of 10%, which will require 58 subjects; however we will aim to enroll 60 subjects (30 per group).
For the second primary aim *anxiety*, we performed two sample size calculations. One based on the data of all 17 patients in the acupuncture group, and another excluding the 3 patients for which protocol deviations were reported due to methods collecting the anxiety measure. With all 17 patients, the difference in the response of anxiety from pre to post acupuncture was normally distributed with a standard deviation 26.27. If the true difference in the mean response of matched pairs is 35.64, we will need to study 6 pairs of subjects to be able to reject the null hypothesis that this response difference is zero with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. With the 3 patients removed, the difference in the response of anxiety from pre to post acupuncture was normally distributed with standard deviation 26.588. If the true difference in the mean response of matched pairs is 39.14, we will need to study 6 pairs of subjects to be able to reject the null hypothesis that this response difference is zero with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05.

Pain is the more appropriate primary outcome of the two primary outcomes to base the sample size on because there are 4 time points of data for each group for this variable. The other primary outcome, *anxiety* does not have a post measure for the control group (per the study design), and therefore a within-group pre to post change in the acupuncture group is being performed to examine this outcome. We acknowledge that this within group design is weaker than the design to assess the pain outcome measure.

Statistical Methods

Patient demographic and clinical (including operative) characteristics will be compared between groups using an independent samples t-test if continuous data are normally distributed), or Mann Whitney U if continuous data are not normally distributed. A chi-square or Fisher's exact test (if cell counts are <5) will be used to compare these characteristics between groups for categorical variables. All continuous variables will be expressed as mean±SD or median, IQR as appropriate. Categorical variables will be expressed as frequency (%).

The primary and secondary study outcomes will be compared between groups two ways. First, an independent samples t-test or Mann Whitney U test if deemed more appropriate for the scale data (which may be considered ordinal) will be used to compare outcomes at each time point between the two groups. Second, a mixed model for repeated measures will be used to compare the study outcomes that are repeated over time (e.g., Pain). This model was chosen instead of a repeated measures ANOVA due to the ordinal nature of the repeated outcome measures in addition to this test being more appropriate for non-normal residuals, missing data, as well as the ability to treat the time points as discrete categories or as true numbers, which accounts for any variability in when the measures are administered to patients.
We anticipate that the timing of the measures being administered may fluctuate slightly due to measures being taken PostOP.

All analyses will be conducted using SPSS version 26.0. P (2-sided) < .05 will be deemed the level of statistical significance.

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Hartford HealthCare

Informed Consent for Research

6816

Principal Investigator: Pranjali Kainkaryam, MD
Anesthesiology
(860) 972-2117

You have been asked to participate in the research study, **Open-Label Randomized Controlled Trial to Assess Preoperative Acupuncture for Patients Undergoing Total Knee or Hip Arthroplasty**.

This research study is expected to last two years. The number of patients expected to be enrolled is 60.

The Hartford HealthCare Institutional Review Board (IRB) has reviewed the information in this consent document and has given approval for the study doctor to do the study. An IRB is an independent committee established to help protect the rights of research subjects. This does not mean the IRB has approved your participation in the study. You must think about the information in this consent document for yourself. You must then decide if you want to be in the study.

KEY INFORMATION FOR *Open-Label Randomized Controlled Trial to Assess Preoperative Acupuncture for Patients Undergoing Total Knee or Hip Arthroplasty*:

We are asking you to choose whether or not to volunteer for a research study about acupuncture given before total knee or total hip replacement surgery, also known as total knee or hip arthroplasty. This page is to give you key information to help you decide whether to participate. We have included detailed information after this page. Ask the research team questions. If you have questions later, the contact information for the research investigator in charge of the study is below.

WHAT IS THE STUDY ABOUT AND HOW LONG WILL IT LAST?

The purpose of this study is to determine whether acupuncture given before total knee or hip replacement surgery reduces anxiety before surgery and pain after surgery in high-anxiety patients. High-anxiety participants in the study, whose anxiety will be determined a week prior to surgery using a validated questionnaire (the Amsterdam Preoperative Anxiety and Information Scale [APAIS]), will be randomized to receive either a short, 30-minute acupuncture procedure before surgery or to receive normal care procedures, also known as the standard of care procedures. These two groups will be compared by several outcomes: the patients' anxiety and pain as well as by their opioid use, nausea and vomiting, and overall satisfaction after surgery.

By doing this study, we hope to learn whether an acupuncture procedure given before total knee or hip arthroplasty is feasible as well as effective for reducing patient anxiety and pain. Your participation in **this research will last about 7 to 10 days, beginning at the time of consent and ending when all outcomes are measured (satisfaction questionnaires may occur post-discharge over the phone)**.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE TO VOLUNTEER FOR THIS STUDY?

The most important reasons you might choose to volunteer for this study are to benefit from the potential anxiety- and pain-reducing effects of the acupuncture treatment. In addition, you may experience a decreased need for pain medication as well as decreased nausea and vomiting after surgery. Overall, you may also experience greater satisfaction with your surgery due to these improvements. Your participation in this study will serve to aid the medical community by allowing further research of a medical intervention.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE NOT TO VOLUNTEER FOR THIS STUDY?

You may not benefit from the procedure, or you may not receive the procedure if you are randomized to the group that will not receive acupuncture. Additionally, there may be risks involved. (see section B on page 4 for risks involved).

DO YOU HAVE TO TAKE PART IN THE STUDY?

If you decide to take part in the study, it should be because you really want to volunteer. You will not lose any services, benefits, or rights you would normally have if you choose not to volunteer.

WHAT IF YOU HAVE QUESTIONS, SUGGESTIONS OR CONCERNS?

The person in charge of this study is Pranjali Kainkaryam (Principal Investigator, PI) from the Hartford HealthCare Department of Anesthesiology. If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study his/her contact information is: Pranjali.Kainkaryam@hhchealth.org (email); (860) 972-2117 (phone).

If you have any questions, suggestions or concerns about your rights as a volunteer in this research, contact representatives from the Hartford HealthCare Human Research Protection Program (HRPP) between the business hours of 8am and 5pm EST, Monday-Friday at 860-972-2893.

A. The Purpose and procedures of this research

A.1. What is the purpose of this research?

The purpose of this study is to evaluate whether acupuncture given before surgery, or preoperative acupuncture, can reduce preoperative anxiety and postoperative pain in high-anxiety patients undergoing total knee or hip arthroplasty surgery.

A.2. What procedures are involved with participation in this research study?

Should you decide to participate in this study, you will finish reading this consent form, ask any questions that you have, and sign the last page. At that point, you will be randomized (like flipping a coin) to receive either acupuncture or standard of care (meaning the care that would be provided to you regardless of your participation in this study) prior to your surgery. You will have a 50% chance of receiving acupuncture before your procedure, or standard of care.

Participants in the acupuncture group will undergo a preoperative acupuncture procedure, which will take place in your preoperative holding bay. First, an acupuncturist will explain the details of the procedure to you. After all questions/concerns are addressed, the acupuncturist will then begin the procedure. The procedure involves the placement of 10 small needles at 5 specific points on each side of your body, including on your ear and wrist, which will be cleaned with alcohol pads beforehand. The needles are inserted roughly 1 millimeter (about 1/25 of an inch) into the skin. It will only last approximately 5 minutes to insert the needles. The needles will then remain inserted for approximately 20 minutes. After the 20 minutes, the needles will be removed by an acupuncturist of the study team, which, in addition to any questions and comments from the patient, will take 5 minutes. The total procedure will last 30 minutes.

Participants in both groups will be required to complete questionnaires and datasheets to measure their anxiety, pain, postoperative nausea and vomiting, and satisfaction. These will occur both in the preoperative area as well as in the postoperative area and over-the-phone if needed.

A.3. Which of these procedures is experimental?

The acupuncture procedure is experimental. Though acupuncture is routinely provided in our facility and others, it has not been provided in our facility immediately before surgery.

A.4. Where will participation take place?

Your study participation will take place at the Bone-and-Joint Institute (BJI) at Hartford Hospital, located at 32 Seymour Street, Hartford, CT 06106.

A.5. How long will participation last?

Your participation is expected to last between 7 to 10 days.

B. The possible risks, discomforts and side effects of the procedures are described below, including safeguards to be used for your protection.

The percentage of patients who experience complications related to acupuncture has been shown to be as high as 6%. The vast majority of complications related to acupuncture are minor and include local bleeding, discomfort, and residual pain at the insertion points. Serious adverse events have been shown to occur in 0.024% of cases (about 2 out of 1,000) and include pneumothorax, abdominal injury, heart injury, central nervous system (CNS) injury, eye injury, neck injury, peripheral nerve injury, and infection. Death related to acupuncture has been reported; though, the frequency of this is so rare that the prevalence is unknown; there have been studies covering more than 3 million acupuncture treatment cases that reported no cases of death related to acupuncture.

All measures will be taken to prevent potential adverse events related to acupuncture. Primarily, this will include having only highly skilled acupuncturists administering the acupuncture treatments. This will also include constant monitoring by the study team.

C. There are possible benefits to you or others to be expected from your participation in this research.

There may be no direct benefit to you for participating in this study.

Participants in this study randomized to receive the acupuncture treatment may experience one or more benefits due to the acupuncture treatment. While this study aims to measure acupuncture's effect on anxiety before and after surgery, acupuncture has already been shown to promote feelings of relaxation and to reduce short-term anxiety immediately after the procedure's completion.

If you receive acupuncture, you may also experience a reduction in anxiety leading to your surgery as well as pain after your surgery, which we expect to find in this study. You may also experience reduced postoperative nausea and vomiting as well as a reduced need for opioids after surgery. Finally, you may also experience greater satisfaction with your overall surgical experience.

If you are randomized to receive standard of care, you will not receive any potential benefits from the acupuncture treatment; however, you will receive the normal standard of care procedures.

D. There are alternatives to participation in this study that you should consider.

Should you decide not to participate in this study, you will receive the standard of care preoperative treatment for your procedure. This may include, should your provider(s) deem it appropriate, the administration of anti-anxiety or relaxation medications prior to procedure.

E. Who can you call if you have questions about this study?

You do not have to sign this consent form until all the questions you have at this time are answered. The investigator is willing to answer any questions you may have about the study procedures. Below is a list of contacts if you should have any questions about the study.

Questions about:	Contact	Phone #
the research, research-related treatments, or a research related injury	Pranjali Kainkaryam, MD	(860) 972-2117
your rights as a research participant	An IRB Representative	(860) 972-2893
a confidential issue that you would like to discuss with someone not associated with research	Patient Advocates	(860) 972-1100

F. Your participation in the research is voluntary.

You may refuse to participate, withdraw your consent, and discontinue participation in the research at any time. You may do so without penalty, or loss of benefits to which you are otherwise entitled. Your decision whether to participate will not affect your future medical care at Harford HealthCare.

G. You will not receive financial compensation for your participation in this research.

H. Your confidentiality will be guarded to the greatest extent possible.

Hartford HealthCare will protect all the information about you and your part in this study, just as is done for all patients at Hartford HealthCare. Your records will be maintained in accordance with applicable state and federal laws. However, private identifiable information about you may be used or disclosed for purposes of this research project as described in the study's authorization form.

Records of your participation in this study will be held confidential to the extent permitted by the applicable laws and regulations, and consistent with the Health Insurance Portability and Accountability Act ("HIPAA") Authorization that you will be asked to sign. The study doctor, the sponsor or persons working on behalf of the sponsor, and under certain circumstances, the United States Food and Drug Administration (FDA), as well as governmental agencies in other countries where the study device may be considered for approval and the Ethics Committee/Institutional Review Board (IRB) will be able to inspect and copy confidential study specific records

which identify you by name. Therefore, absolute confidentiality cannot be guaranteed. If the results of this study are published or presented at meetings, you will not be identified.

I. What happens if you are injured as a direct result of your participation in this research project?

In the event that you are injured as a direct result of taking part in this research, you will receive help in the following way:

If you have medical insurance, Hartford HealthCare will collect fees for medical treatment at Hartford HealthCare from your insurance company. If you are not fully covered by insurance or uninsured, the research sponsor of the study or Hartford HealthCare will cover these expenses.

There is no plan for Hartford HealthCare to pay for your medical expenses at other hospitals or for pain and suffering, travel, lost wages, or other indirect costs of taking part in this research. You do not waive any of your legal rights by signing this informed consent document.

J. Signatures

You will be given a copy of this informed consent document to keep. By signing below, it means that you have read it, that you voluntarily agree to participate in this research, **Open-Label Randomized Controlled Trial to Assess Preoperative Acupuncture for Patients Undergoing Total Knee or Hip Arthroplasty**, and that you consent to the performance of the procedures listed above.

Participant's Signature	Printed Name	Date

Person Obtaining Participant's Signature	Printed Name	Date

Witness signature	Printed Name	*Date*

(A witness is the person observing the explanation of the above information to the participant. A witness to the informed consent process is optional unless presented orally.)