Title
Feasibility of Electro Auricular Acupuncture for Analgesia after ACL surgery: The feasibility of patient blinding and effects on early postoperative pain

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Title:
Feasibility of Electro Auricular Acupuncture for Analgesia after ACL surgery: The feasibility of patient blinding and effects on early postoperative pain

What is the condition or intervention being studied?
We will investigate the feasibility of blinding patients to intraoperative acupuncture for analgesia after ACL surgery.

What is/are the research question(s)/specific aim(s)?
Feasibility measures:
1. How successful will blinding be in the acupuncture and control groups?
2. What percentage of eligible patients will agree to participate in the trial?
3. In what percentage of cases will the equipment and practitioner be available immediately after the patient reaches sedation?
4. In what percentage of cases will intraoperative time be sufficient for needle placement and stimulation?
5. What are the variability (e.g., standard deviation) and missing data patterns of the following outcome measures?
Outcome measures:
- NRS Pain scores
- Opioid consumption
- Patient satisfaction with pain treatment
- Nausea intensity
- Vomiting intensity

What is/are the hypothesis(es)?
Our hypothesis it that it will be feasible to blind ACL Surgery patients to whether or not the received intraoperative acupuncture.

The success of patient blinding in each group will be quantified using the Bang Blinding Index (Bang 2010), which ranges from -1 (complete opposite guess) to 1 (complete unblinding). Blinding Indices (BI) will be categorized as $BI \geq 0.2$ (unblinded), $-0.2 < BI < 0.2$ (random guess), and $BI \leq -0.2$ (opposite guess) (Moroz 2013). We will conclude blinding to be feasible if we can rule out the following scenarios (via calculation of the limits of the 95% confidence intervals for the BIs): (1) unblinding in both arms, or (2) unblinding in the acupuncture arm and random guessing in the no acupuncture arm (Moroz 2013).

References
1. Bang H, Flaherty SP, Kolahi J, Park J. Blinding assessment in clinical trials: A review of statistical methods and a proposal of blinding assessment protocol. Clin Res Regul Aff 2010; 27:42-51
2. Moroz A, Freed B, Tiedemann L, Bang H, Howell M, Park JJ. Blinding measured: a systematic review of randomized controlled trials of acupuncture. Evid Based Complement Alternat Med 2013;2013: 708251.

Primary outcome
The primary outcome is patient blinding. On POD1, patients will be asked "Do you believe you received acupuncture or no acupuncture?" with the following answer options: "acupuncture" "no acupuncture" or "don't know".

Identify and define the secondary outcome(s) and when they will be measured
Feasibility measures:
- Patient agreement to participate in trial
- Sufficient time for needle placement & needle stimulation

Outcome Measures
- NRS pain scores at rest and with movement (POD0, POD1)
- Opioid consumption (POD0-POD1 - 24 hours from anesthesia end)
- Patient satisfaction with pain treatment (POD1)
- Nausea intensity (0, 30, 60, 90, and 120 min after PACU admission on POD0)
- Vomiting intensity (0, 30, 60, 90, and 120 min after PACU admission on POD0)

Explain why these research questions are being asked:
According to the most recent survey conducted by the national center for complementary and integrative health (a branch of the National Institutes of Health) in 2007, the use of complementary alternative medicine (CAM) has increased significantly from 2002 (the previous survey). In the 2007 survey, in the United States alone, 38% percent of adults and 12% of children use some form of CAM. It has been 10 years since that survey report, there is little doubt that these numbers have only increased. According to the National Center for Health Statistics on the expenditures on CAM in 2012 – for just adults utilizing specialists, such as acupuncturists, $14.1 Billion was spent. With this increasing demand of such treatment modalities by patients, conventional practitioners will need to be, at the very least, well versed enough to recommend for or against these modalities. In addition, the current opioid epidemic is on the forefront of the public mind. Recently declared a public health emergency by the President, alternative means of post-operative pain control is a necessity and integrative medicine is a low cost, safe, and effective adjuvant/alternative.

Particularly in the perioperative setting, acupuncture can be helpful by increasing a patient's endorphin levels to help with anticipated surgical pain, decrease anxiety, and overall health (Han JS, et al). Because surgery is traumatic to the body, maximizing emotional and physical wellbeing is advantageous for a good post-surgical outcome. Intraoperatively and post operatively, it has been found to be a useful adjuvant for pain control. Additionally, it can also help with many of the other side effects of surgery including post-operative nausea/vomiting, constipation, urinary retention, and headache (Helms).

Acupuncture research with regards to PONV has been fairly well established that acupuncture with pericaridum 6 (PC6) is equivalent to the use of pharmacologic antimetics. (Lee A, et. Al.) Studies about perioperative pain control and acupuncture are a little more murky. A meta analysis in 2008 looked at randomized controlled studies and found that while acupuncture was shown to decrease pain, there were several limitations including the continued issue of a credible placebo or sham intervention and thus blinding. This analysis only included studies where the control group did receive a placebo or sham intervention. (Sun et. Al). Given the known ability of sham acupuncture to create even a marginal effect makes it impossible to determine whether or not the acupuncture intervention showed a true improvement and to what level.

The main purpose of this feasibility trial is to determine whether or not adequate blinding is possible in the intraoperative setting with the patient sedated. If it is feasible, then it would allow

for a true standard of care control group to compare the acupuncture intervention group to with the future goal of performing a randomized controlled trial to formally test whether intraoperative electro auricular acupuncture can provide superior analgesia.
In addition, there have been a paucity of studies utilizing solely Auricular Electro -acupuncture as a means of treatment. Like PC6, body points are often not accessible intraoperatively and it is therefore our goal to study the Ear microsystem as that is readily available in most orthopedic surgeries.

References

1. Hans JS. Acupuncture and endorphins. Neuroscience Letters 2004; 361; 258-261.
2. Helms JM. Acupuncture Energetics: A Clinical Approach for Physicians. Berkeley, Calif: Medical Acupuncture Publishers; 1995
3. Lee A, Chan SK, Fan LT. Stimulation of the wrist acupuncture point pc6 for preventing postoperative nausea and vomiting. Cochrane Database Syst Rev 2015:CD003281.
4. Sun Y, Gan TJ, Dubose JW, Habib AS. Acupuncture and related techniques for postoperative pain: A systematic review of randomized controlled trials. Br J Anaesth 2008;101:151-60.

What is the background of the topic that you believe is important for the reviewer to know in considering this protocol, including prior studies by this research team. Describe strengths and deficiencies or prior studies; explain how this study fits in. Include references.

The Joint Commission has issued a new statement effective Jan 2018 with regards to “New and revised standards as related to pain assessment and management” of which part of their elements of performance and requires that all accredited hospitals provide access to nonpharmacologic modalities of pain management. Acupuncture is an example of a nonpharmacologic pain management modality that has been shown to provide superior analgesia for acute pain compared to no acupuncture, sham acupuncture, and opioids in previous trials (Lin, et al). However, in all previous trials acupuncture has been performed either pre or post operatively, potentially compromising blinding. While sham acupuncture may possibly ameliorate the blinding issue, it may have an analgesic effect on its own (Vincent et. Al.). Performing acupuncture intraoperatively may allow for adequate blinding without risking the effect of a sham. In any clinical trial involving blinding with a placebo control, the patient should not be able to tell the difference between receiving the treatment and not receiving the treatment. The control placebo itself should not change any physiology within the patient. For acupuncture, meeting both criteria is difficult to accomplish at the same time (Chae, et. Al.) given the invasive nature of treatment.

Our future goal is to perform a randomized controlled trial to formally test whether intraoperative electro auricular acupuncture can provide superior analgesia after ACL surgery compared to no acupuncture while maintaining adequate blinding. The main purpose of this feasibility trial is to determine whether such a trial would be feasible with respect to adequate blinding, patient accrual, and ability to administer the intervention.

Recently, ATP (auricular trauma protocol) has been replacing Battlefield Acupuncture (BFA) with an increased effectiveness for a number of syndromes. In speaking with Joseph Helms, he has anecdotally seen its effectiveness and it is time to back that with research. Therefore we will be utilizing ATP points for this study. (Helms, et al. 2011)

References
1. *Chae Y, Lee Y-S, Enck P. How placebo needles differ from placebo pills? Frontiers in Psychiatry 2018;9.*
2. *Vincent C, Lewith G. Placebo controls for acupuncture studies. J R Soc Med 1995;88:199-202.*

Identify specific gaps in current knowledge that this study is intended to fill.
It is unknown whether it is feasible to blind ACL surgery patients to whether or not they received intraoperative acupuncture.

How will answering these questions change clinical practice, change concepts about the topic or confirm the work of other investigators?
If results of this feasibility study show that blinding ACL surgery patients to intraoperative acupuncture is feasible, then the analgesic efficacy of intraoperative acupuncture can be tested in future randomized controlled trials without the concern of inadequate blinding potentially biasing results.

Is this a pilot study that could lead to a more definitive protocol or different study?
Yes

Experimental
Other: This is a feasibility study

Inclusion criteria:
-Patients undergoing ACL surgery with a participating surgeon
-Patients at least 12 years old
-Planned spinal anesthesia without peripheral nerve block (rescue nerve block is okay if necessary)
-English speakers

Exclusion criteria:
- Patients under the age of 12
-Non-English speakers
-Patients planning on having general anesthesia
-Planned preop peripheral nerve block (rescue nerve block is okay and is not an exclusion)
- Patients with the inability to understand/follow study protocol
- Patients with pacemaker/AICD
- Active ear infection
- Non-native Ear/Previous scarring/surgical manipulation of Ear
- Patients with contraindications to intra-op protocol
- Chronic pain patients
- Patients who have regularly used opioids for more than 6 weeks prior to surgery
- Patients with gauges in their ears
- Patients who refuse to remove earrings/piercings prior to surgery
- Patients with Nickel allergies (needles are made of nickel)

Age range:
At least 12 years old

Describe how you will identify and recruit potential subjects for participation in the study.
The research assistant will identify patients the night before their surgery by reviewing the OR schedule. Patients will be approached in the holding area on the day of their surgery by a co-investigator who will explain the study in detail. Written consent (and assent when applicable) will be obtained by a co-investigator in the holding area prior to the procedure once all questions are answered and after the patient understands the protocol. No Compensation will be offered. In the event that a patient is under 18, they will only be approached if there is at least 1 parent/legal guardian in the holding room. Patients under 18 will provide written assent while their parent/legal guardian will provide a signature for the assent and consent forms.

Please select enrollment type from following drop down list:
Over course of Study

Target enrollment
40

What is the maximum number of subjects you plan to enroll in this study?
40

How subjects will be identified

- Potential subjects will be identified after a review of medical records of patients under the care of one or more of the study investigators
- Medical records and/or other Institution sources (databases,registries,billing records,pathology reports,admission logs) will be reviewed to identify potential participants. May involve access of records by individuals not involved in the patient's care.

Eligible patients will be approached in the holding area prior to their procedure on the day of surgery by a co-investigator (MD or Research Assistant). The study will be explained to them in detail and written consent (and assent when applicable) will be obtained after all questions have been answered.
Patients under the age of 18 will only be approached if/when a parent/legal guardian is present in the room. Minors will only provide assent while their parent/legal guardian will sign both the consent and assent forms.

Data will be collected:

Day of Surgery Preoperatively (from medical chart and patient interview)

a. Patient demographics – date of birth, race, ethnicity, gender, ASA level, BMI, prior experience with acupuncture, prior piercings
b. Numeric Scale Rating (NRS) Pain Scores

Day of Surgery Intraoperatively (from medical chart)

a. Level of sedation

Day of Surgery Postoperatively (from medical record and patient report)

a. NRS Pain scores (every 30 minutes until 120 minutes)
b. Nausea/vomiting assessment (every 30 minutes until 120 minutes)
c. Opioid consumption
d. Blinding assessment

Postoperative Day 1 (from patient report)

a. NRS Pain Scores
b. Nausea/Vomiting assessment
c. Opioid consumption
d. Blinding assessment
e. Patient satisfaction

Sample Size and Data Analysis:

Instruments and questionnaires to be used on this study:

- Bang's Blinding Assessment
- Nausea and Vomiting Assessment
- NRS Pain Scale

Describe any risks to participants in the Placebo or No-Treatment Arm of the Study
This study uses a no-acupuncture arm. The patients in the no-acupuncture group have already agreed to our standard anesthetic/analgesic regimen. The addition of no-acupuncture group does not add any additional risks.

Provide a Scientific or ethical justification for using a placebo or No-Treatment arm
Patients are randomized to receive acupuncture or no acupuncture. The no acupuncture group is the same standard of care that the patients would receive if not enrolled in the study. Since the protocols for both groups are otherwise identical, any differences between the groups may be attributed to whether or not patients think they have received acupuncture. However, we don't know the benefit of intraoperative acupuncture. At this time we are looking at the feasibility of blinding to ensure that future studies will be able to be performed with regards to intraoperative acupuncture

Sample size and data analysis:

Is this a case series based only on the patients available using descriptive statistics in lieu of a sample size calculation?
No

Data analysis:

1. **Proposed analysis (e.g., student's t-test, ANOVA, chi-square, regression, etc.):** Calculation of Bang Blinding Index (Bang 2010) with 95% confidence interval for the acupuncture arm
2. **Interim analysis planned?** No
3. **Alpha level:** 0.05 (two-sided)
4. **Beta or power level:** N/A
5. **Primary outcome variable estimate (mean +/- s.d. for continuous outcome, frequency/percentage for categorical variable):** Expected proportion of patients in acupuncture arm who will guess that they were assigned to the acupuncture arm = 0.1
   Expected proportion of patients in acupuncture arm who will guess that they were assigned to the control arm = 0.1
   Bang Blinding Index in acupuncture arm = 0.1 – 0.1 = 0
   We would like to estimate the Bang Blinding Index in the acupuncture arm ± 0.2
6. **Number of groups being compared (use 1 for paired analysis within the same subjects):** N/A

7. **Effect size or change expected between groups:** N/A
8. **Resulting number per group:** 20 (Landsman 2017)
9. **Total sample size required:** 40
10. **Who conducted your sample size calculation?** Kara Fields

Continuous variables will be summarized as means with standard deviations or medians with 1st and 3rd quartiles, depending upon the distribution of the data. Ordinal variables will be summarized as medians with 1st and 3rd quartiles or frequencies and percentages, depending upon the distribution of the data. Binary variables will be summarized as frequencies and percentages.

The success of patient blinding in each group will be *quantified* using the Bang Blinding Index (Bang 2010), which ranges from -1 (complete opposite guess) to 1 (complete unblinding). Blinding Indices *(BI)* will be categorized as BI ≥ 0.2 (unblinded), -0.2 < BI < 0.2 (random guess), and BI ≤ -0.2 (opposite guess) (Moroz 2013). Adequate blinding will be concluded if we can rule out the following scenarios *(via calculation of the limits of the 95% confidence intervals for the BIs):* (1) unblinding in both arms, or (2) unblinding in the acupuncture arm and random guessing in the no acupuncture arm (Moroz 2013).

Between-group effect sizes will be calculated as differences in means, differences in medians, or relative risks with 95% confidence intervals. No P values will be calculated.

References

1. Bang H, Flaherty SP, Kolahi J, Park J. Blinding assessment in clinical trials: A review of statistical methods and a proposal of blinding assessment protocol. Clin Res Regul Aff 2010; 27:42-51
2. Landsman V, Fillery M, Vernon H, Bang H. Sample size calculations for blinding assessment. *J Biopharm Stat*. 2017;3406:1-13.
3. Moroz A, Freed B, Tiedemann L, Bang H, Howell M, Park JJ. Blinding measured: a systematic review of randomized controlled trials of acupuncture. Evid Based Complement Alternat Med 2013;2013: 708251.

Describe how, when, and where the consent process will be initiated:

Eligible patients will be approached in the holding area prior to their procedure on the day of surgery by a co-investigator (MD or Research Assistant). The study will be explained to them in detail and written consent (and assent when applicable) will be obtained after all questions have been answered.

Patients under the age of 18 will only be approached if/when a parent/legal guardian is present in the room. Minors will only provide assent while their parent/legal guardian will sign both the consent and assent forms.