Femoral Peri-arterial Local Anesthetic Injection Decreases Tourniquet Associated Ischemic Hypertension.

NCT03390426

Research Summary Version Date: 1/8/2018
Uploaded in Current Form: 10/2/2019

1. Protocol Title:

Femoral Peri-arterial Local Anesthetic Injection Decreases Tourniquet Associated Ischemic Hypertension.

2. Purpose of the Study:

The goal of this prospective randomized double-blind study is to determine if an ultrasound guided peri-arterial injection of local anesthetic around the femoral artery decreases ischemic hypertension associated with prolonged lower extremity tourniquet time. Efficacy will be determined by analyzing incidence of intraoperative ischemic hypertension, defined as $\geq$30% increase in systolic blood pressure, associated with tourniquet inflation times greater than 90 minutes. Secondary outcomes will include post-operative numerical pain scores (NRS 11) and perioperative opioid consumption. English speaking ASA 1-3 patients ages 18-75 years old undergoing total ankle arthroplasty (TKA) will receive both popliteal-sciatic and adductor canal nerve blocks with perineural catheters with 0.2% ropivacaine preoperatively. Patients will then undergo femoral peri-arterial injection with either 1.5% mepivacaine with 1:400,000 epinephrine or 0.9% saline. Data will be analyzed on an intent to treat basis using a two-sided t-test (parametric) or Mann-Whitney-Wilcoxson (non-parametric) with a p-value $\leq$0.05 as significant.

3. Background & Significance:

The use of pneumatic tourniquets to provide a bloodless field is a common technique in orthopedic surgery. Although typically well tolerated initially, prolonged tourniquet duration over 60 minutes often leads to marked increases in both heart rate and blood pressure [1]. This phenomenon has been referred to as tourniquet hypertension. Incidence varies depending on tourniquet time, location, and site of tourniquet [1] . In a retrospective study of 699 patients undergoing surgery with a pneumatic tourniquet, the general anesthesia subgroup had an incidence of 66.7% [2]. Through these studies, tourniquet hypertension has been defined as an increase in either systolic or diastolic blood pressure (SBP or DBP) 30% above baseline.

Etiology of tourniquet hypertension is controversial and not completely understood. Tourniquet pain is thought to arise from uninhibited C fiber activation in the context of decreased inhibition from A-δ fibers. A-δ fibers are inhibited by mechanical compression caused by the tourniquet [3]. Some authors have argued tourniquet pain comes from compression of skin and have shown subcutaneous local infiltration and EMLA cream can improve tolerance of tourniquet [4, 5]. Despite these observations, tourniquet pain and hypertension can be present even with adequate sensory levels during spinal and epidural anesthesia [6]. Another study has shown that combined femoral and proximal sciatic nerve blockade does not reduce incidence of tourniquet hypertension when compared to femoral and popliteal sciatic nerve blocks in surgeries utilizing a below knee tourniquet [7].

A possible reason for tourniquet pain and hypertension despite appropriate peripheral nerve blockade may be due to the location of the sympathetic nerve fiber afferents, including C fibers, which are carried on the femoral artery [8]. For this reason, we propose an injection of local anesthetic between the femoral artery and femoral vein would block perivascular sympathetic nerve fibers. In a small pilot study of 10 patients undergoing TKA who received

periarterial local anesthetic, we found that tourniquet hypertension, which we define as an increase in SBP of 30% above baseline, was prevented in all patients.

4. Design & Procedures:

Preoperatively, patients will be given 975mg acetaminophen by mouth. This medication may be altered or omitted depending on patient comorbidities or extenuating factors such as allergy/intolerance. Study interventions will begin preoperatively. Patients will receive up to 2mg midazolam IV and 100mcg fentanyl IV. As standard of care at Duke Hospital, patients will then undergo ultrasound guided adductor canal and popliteal sciatic peripheral nerve blocks with 20 mL of 0.2% ropivacaine plus insertional of perineural catheters for post-operative analgesia.

Patients will be randomized into either femoral peri-arterial block or sham group with an online randomization program by the study PI (WMB) prior to any patient enrollment. Patients will be given a unique study number (1-30), and the randomized numbers will be given to a key study personnel member (JG) that will be unblinded. The intervention drug, either 10mL 1.5% mepivacaine with 1:400,000 epinephrine for block group or 10mL 0.9% saline for sham group, will be drawn up by a key personnel member of the study team who is unblinded and will not be involved in the femoral peri-arterial block or post-operative analysis. This person will supply the regional anesthesiologist with the intervention, however, both the regional anesthesiologist performing the block and the patient will be blind as to the contents of the syringe.

Patients will then be taken to the operating room where they will undergo general anesthesia for the surgical procedure. General anesthesia is the standard of care for foot and ankle surgery. Induction will consist of 1-2mg/kg IV propofol after which a laryngeal mask airway (LMA) will be placed. Maintenance will be achieved with sevoflurane. A bispectral index (BIS) monitor will be used and sevoflurane will be titrated to a BIS value between 40 and 60. After induction, a bolus of 10mg IV dexamethasone (will not be given in diabetic patients) will be administered.

Presence of tourniquet hypertension, defined as an increase in systolic or diastolic blood pressure by 30% or more during tourniquet inflation will be recorded. Esmolol will be given in 20mg boluses if SBP rises >30% baseline, and will be given until SBP returns to normal (<20% baseline). At conclusion of the case, LMA will be removed and the patient will be taken to post-operative care unit (PACU).

In PACU, patients will have post-operative orders for supplementary pain control that include 0.2mg IV hydromorphone for pain scores 5-7 and 0.4mg IV hydromorphone for pain scores 8-10. Subjects' verbal pain scores and opioid consumption will be recorded every half hour until discharge from PACU. Additionally, gross motor function for both quadriceps will be assessed 1 hour after extubation. These scores will be entered into a Duke REDCap database.

5. Selection of Subjects:

ASA 1-3 patients aged 18-75 years old undergoing total ankle arthroplasty or foot fusion will be enrolled. Patients will be identified preoperatively in either preoperative screening clinic or the night prior to surgery depending on method of preoperative screening. Patients in the study will be ASA 1-3 patients, many will be screened by phone instead of a clinic visit. Patients not seen in preoperative screening clinic will be contacted by telephone by primary investigator (WMB) to confirm eligibility and, if eligible and interested, the study will be explained. Patients will be given the opportunity to ask initial questions about the study over the phone. Patients interested in participating will be again have the protocol fully explained and written informed consent will be obtained on the day of surgery prior to receiving any sedation. The patient's care team, including attending surgeons, attending anesthesiologists, residents, and nurse anesthetists will be informed of the patient's inclusion via secure email with specifics for the case.

Inclusion Criteria:

Patients that will be included in the study are English speaking 18-75 year old ASA 1-3 patients undergoing total ankle arthroplasty or ankle fusion procedures.

Exclusion Criteria:

Patients will be excluded from the study if they meet one or more of the following Criteria:

1) ASA 4 or 5

2) Diagnosis of chronic pain

3) Daily chronic opioid use (over 3 months of continuous opioid use).

4) Inability to communicate pain scores or need for analgesia.

5) Infection at the site of block placement

6) Age under 18 years old or greater than 75 years old

7) Pregnant women (as determined by point-of-care serum bHCG)

8) Intolerance/allergy to local anesthetics

9) Weight <50 kg

10) Suspected, or known addiction to or abuse of illicit drug(s), prescription medicine(s), or alcohol within the past 2 years.

11) Uncontrolled anxiety, schizophrenia, or other psychiatric disorder that, in the opinion of the investigator, may interfere with study assessments or compliance.

12) Current or historical evidence of any clinically significant disease or condition that, in the opinion of the investigator, may increase the risk of surgery or complicate the subject’s postoperative course.

6. Subject Recruitment & Compensation:

Only patients who are having total ankle arthroplasty or foot fusion are eligible for this study. We will not bias any demographic groups in identifying patients eligible for this study. A total of 30 patients will be consented from Duke University Medical Center. An IRB approved phone script may be used to discuss the study with eligible patients missed at their Pre-Op screening visit. Patients will not receive any additional compensation for enrollment in this study.

7. Consent Process

A patient's permission to be approached for research will be obtained by the primary care team involved with the patient. The consent process will be conducted by the research personnel or one of the physicians involved in the study. The consent process will take place in the pre-operative screening or the surgical clinics. Throughout the consent process, measures will be taken to maintain privacy, such as by conducting face-to-face conversations in private rooms. As much time as necessary will be spent with each potential subject to sufficiently explain and answer all questions, and address all concerns they may have in regard to the study and/or consent process. Under HIPAA waiver, the study team will identify potential subjects from clinic schedules, OR schedules and Maestro Care.

8. Subject's Capacity to Give Legally Effective Consent:

Patients who do not have the capacity to give legally effective consent will not be approached for participation in this study.

9. Study Interventions:

See 4 above.

10. Risk/Benefit Assessment:

Patients will not incur any added risk to standard risks incurred with both general and regional anesthesia. These standards risks are:

- General anesthesia - includes sore throat, hoarseness, injury to teeth, mouth, airway or eye, infection, pneumonia or other lung problem, injury to arteries or veins, allergy or adverse drug reactions, nausea, vomiting, awareness under anesthesia, brain damage, nerve injury or paralysis, and/or loss of life;
- Regional anesthesia - minor pain or discomfort, injury to arteries, veins or nerves affecting the arms or legs, residual numbness or weakness or paralysis, headache, muscle soreness, infection, allergy or adverse drug reaction, intravascular injection of local anesthetic causing seizure or cardiac arrest.

Benefits include contributing to general knowledge base to improve future patient care. This includes potential confirmation of analgesic benefit, improved control of hemodynamics during anesthetic, decreased pain scores, and improved patient satisfaction. Conversely, this study may show no benefit of the block, thereby invalidating the technique.

11. Costs to the Subject:

Subjects will not incur any additional costs to participate in the study. A MaestroCare build will be created to ensure that any subjects are not charged for researched related procedures, equipment, or medications.

12. Data Analysis & Statistical Considerations:

A double blinded randomized trial of 30 subjects (15 per group), assuming a rate of hyperextension of 20% in the placebo group, will provide 82% power to detect a 50% decrease in the rate of tourniquet hypertension in the treatment group in a chi-square test at alpha level 0.05. Sample size and power calculations were performed using PASS v15 (NCSS, LLC. Kaysville, Utah).

Patient and surgical characteristics will be summarized by standard descriptive statistics and will be compared between groups using t-tests, Wilcoxon rank sum tests, chi-square tests, or Fisher exact tests as appropriate. A chi-square test and logistic regression models will be used to assess the effect of treatment on rate of hyperextension. We will report odds ratios, 95% confidence intervals, and p-values to assess significance and clinical importance of the observed treatment effect. Additional measures of treatment efficacy (range of motion, pain scores, and opioid consumption) will be summarized overall and between groups to further characterize the treatment effect in this population. Randomization schedules will be prepared using mixed block sizes in nQuery and significance will be set at 0.05 for all analyses.

13. Data & Safety Monitoring:

In accordance with federal regulations the PI will monitor for, review, and promptly report to the IRB, appropriate institutional officials, sponsor, coordinating center and the appropriate regulatory agency head all unanticipated problems involving risks to subjects or others that occur in the course of a subject's participation in a research study (45 CFR 46.103(b)(5)(i) and 21 CFR 56.108(b)(1)), all AE reports will be reported per the DUHS IRB policies. PI will be monitoring all AEs and submitting reports to the IRB per DUHS IRB policy.

14. Privacy, Data Storage & Confidentiality

Potential subjects and their families will be approached in private rooms. Any guests not involved in the consent process will be asked to leave the room during any such communications, unless the patient allows them to be present. Efforts to maintain subject confidentiality will include following Federal Privacy Regulations which provide safeguards for privacy, security, and

authorized access. Except when required by law, subjects will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of Duke University Health System (DUHS). Subjects will not be revealed in any reports or publications resulting from this study. For records disclosed outside of DUHS, subjects will be assigned a unique code number. The paper and electronic data will be stored as per the RDSP.

REFERENCES:

1. Gielen, M.J. and R. Stienstra, *Tourniquet hypertension and its prevention: a review.* Reg Anesth, 1991. **16**(4): p. 191-4.
2. Valli, H., et al., *Arterial hypertension associated with the use of a tourniquet with either general or regional anaesthesia.* Acta Anaesthesiol Scand, 1987. **31**(4): p. 279-83.
3. Hodgson, A.J., *A proposed etiology for tourniquet-induced neuropathies.* J Biomech Eng, 1994. **116**(2): p. 224-7.
4. Tsai, Y.C., Y.Y. Lai, and C.L. Chang, *Comparison of the effect of EMLA cream, subcutaneous ring anaesthesia and a double cuff technique in the prevention of tourniquet pain.* Br J Anaesth, 1993. **70**(4): p. 394-6.
5. Rousso, M., et al., *Subcutaneous ring anaesthesia in the prevention of tourniquet pain in hand surgery.* Hand, 1978. **10**(3): p. 317-20.
6. Bonnet, F., et al., *Prevention of tourniquet pain by spinal isobaric bupivacaine with clonidine.* Br J Anaesth, 1989. **63**(1): p. 93-6.
7. Fuzier, R., et al., *Does the sciatic nerve approach influence thigh tourniquet tolerance during below-knee surgery?* Anesth Analg, 2005. **100**(5): p. 1511-4, table of contents.
8. Singh, I., *Textbook of anatomy*. 5th ed. 2011, New Delhi: Jaypee Brothers Medical Publishers.