Perineural steroids for saphenous peripheral nerve blocks: An equivalency dosing study

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Short Title:
Perineural steroids for peripheral nerve blocks

Study Full Title:
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Principal Investigators, Co-investigators:
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Summary/Purpose/Rationale
Regional anesthesia techniques are common modalities used to provide analgesia following both upper and lower extremity surgeries. Many different combinations of adjuvants added to local anesthetics for peripheral nerve blocks (PNB's) have been attempted to prolong the duration of analgesia following surgery. These adjuvants include clonidine, buprenorphine, tramadol, midazolam, and neostigmine [1].]. In some preliminary studies, dexamethasone appears to prolong the duration of analgesia in both the perineural route and intravenous route [2, 3]. However, many of these studies were based on subjective primary end points, such as quality of recovery surveys or time to first opioid analgesic request [3,4]. Interestingly, a study out of Toronto has more completely shown what was already seen in preliminary studies, that both systemic and perineural steroids are also effective in prolonging the duration of peripheral nerve blocks [5, 6].

Dexamethasone, a glucocorticoid with minimal mineralocorticoid effect, has been shown to improve the overall quality of surgery in certain surgical populations as well as decrease the amount of opioid consumed when given intravenously [7]. Though there has been some concern regarding the potential neurotoxicity of dexamethasone, there have been multiple studies that purport to show no neurotoxic findings with single injection dexamethasone alone or in combination with local anesthetics as single injection doses [8, 9]. However, there have been limited human studies giving safety data [2]. Given this concern, it is paramount to determine if an effective lengthening of the peripheral nerve block can be accomplished with a lesser dose [10]. Many studies have used 4 mg and 8mg of dexamethasone perineurally, but none to our knowledge have compared a lower dose to see if it is equally effective while limiting potential neurotoxicity concerns [2]. The saphenous nerve would be an ideal nerve to study given that it is a sensory nerve with no motor function.

Objectives
The purpose of this randomized, double-blinded, placebo-controlled trial is to examine if dexamethasone given perineurally as an adjuvant to the nerve block will prolong the time to recovery from sensory nerve block. We hypothesize that dexamethasone will provide analgesic times greater than that seen in the control arm without dexamethasone, and that similar results will be obtained by the 1 mg arm when compared to the 4 mg arm. The primary outcome will be

time to resolution of the nerve block as assessed by pinprick over the saphenous nerve distribution. Secondary outcomes will include pain scores, amount of post-operative opioids, and the incidence of nausea and vomiting will be recorded over the course of 24-48hrs. This will be done by asking the patient about nausea and emesis following recovery. The answers will be recorded on the data sheet as yes or no. Subjects will also be followed to evaluate for potential neurologic complications such as persistent paresthesias in the distribution of the saphenous nerve.

Methods/Measurements:

Design:

This study will be a randomized, double-blind, placebo-controlled trial that will take place after Institutional Review Board approval. Written informed consent will be obtained from all the study participants. We have already obtained an Investigational New Drug (IND) exemption from the Food and Drug Administration (IND 125810) for this study given the following protocol

Selection Criteria:

Inclusion: Adults, between 18 and 90 years of age, undergoing elective robotic medial and/or patellofemoral MAKO partial knee arthroplasty and who have agreed to a regional anesthesia technique will be recruited to participate.

Exclusion: Subjects with contraindications to regional anesthesia, such as a history of allergy to amide local anesthetics, presence of a progressive neurological deficit, a pre-existing coagulopathy, infection, or the following conditions: insulin and non-insulin dependent diabetes mellitus, systemic use of corticosteroids within 30 days of surgery, chronic use of an opioid analgesic (>3 months or a combined total of more than 40 mg Oxycodone equivalents a day), or whom are pregnant will be excluded. Also, any patient with a prior history of an adverse event (for example: psychosis) or an allergy to dexamethasone will be excluded.

Setting**:**

All patients in the study will be undergoing non-urgent surgery at Wake Forest University Baptist Medical Center. The interventions will be performed in the regional anesthesia area of the surgery center.

Interventions and Interactions:

Adults, between 18 and 90 years of age, undergoing elective robotic medial and/or patellofemoral MAKO partial knee arthroplasty will be recruited to participate. Eligible patients will be identified the day before surgery based on surgical postings. Upon arrival to the regional anesthesia area of surgical services at Wake Forest University Baptist Medical Center they will be formally consented if they are interested in participating in the study. Patients will be asked to provide baseline verbal pain scores both at rest and with movement on a scale of 0-10 (0 being no pain and 10 being the worst pain). Preoperative opioid use including drug, dosage and frequency will be recorded. Additionally, baseline patient characteristics will be recorded including height, weight, BMI, sex, age, surgeon and operative side.

Before PNB placement each patient will be randomized blindly to one of the three aforementioned arms. Blinding will occur by a secondary provider in the regional and acute pain management area by a second provider not associated with the study. This will obviously occur following randomization. All volumes will be identical. Once randomization and blinding occur, standard ASA monitors and oxygen will be applied. All saphenous nerve blocks will be performed by a resident or a fellow trainee supervised by an attending anesthesiologist. Sedation for the PNB will be provided in the usual manner at the discretion of the anesthesiologist providing the nerve block. Unless there is a contraindication, each patient will receive 1000 mg of PO acetaminophen, 150 mg of PO pregabalin, and 400 mg of celecoxib.

All subjects will receive an ultrasound-guided adductor canal nerve block and will be computer randomized to receive 20 ml of one of the following solutions: either 0.25% bupivacaine with epinephrine 1:400,000, 0.25% bupivacaine with epinephrine 1:400,000 with 4 mg of preservative free dexamethasone added to the solution, or 0.25% bupivacaine with epinephrine 1:400,000 with 1 mg of preservative free dexamethasone added to the solution. Both the subject and the investigator will be blinded to the arm of the study.

The products to be used are the following, and have been granted an FDA IND exemption (IND 125810)
1) Bupivacaine Hydrochloride. 30 ml single dose vial. 11 Digit NDC code: 00409-1159-02. Hospira, Inc. Lake Forest, IL.
2) Dexamethasone Sodium Phosphate Injection 10mg/ml. APP Pharmaceuticals LLC, Schaumburg, Ill. NDC Code: 63323-506-01, 63323-516-10
3) McKesson ID 2070274 Adrenalin Chl. Inj. 1mg/ml 1ML25 epinephrine NDC 2023015925.

For each nerve block, the epinephrine will be added to the bupivacaine and dexamethasone in a sterile fashion and used within 24 hours of the epinephrine being added. Otherwise, the solution will be discarded. All procedures will be performed under a sterile technique including the use of a chlorohexidine prep of the skin, sterile gloves, a sterile ultrasound probe cover with sterile ultrasound gel, and a cap and a mask. A 21-gauge 90 mm Arrow StimuQuick, stimulating needle (Teleflex, USA) will be directed under real-time ultrasound guidance into the adductor canal. The local anesthetic solutions will be injected incrementally in 5 mL aliquot to a total volume of 20 mL to surround the saphenous nerve.

Study subjects will receive either a spinal anesthetic with propofol sedation (25–100 μg/ kg/min) or a general anesthetic for their surgical procedure. Patients will undergo their surgery and be brought to the post-anesthesia recovery unit (PACU). The patient will remain in the PACU until resolution of the spinal from the non-operative side.

These participants will be observed overnight and will be evaluated every two hours with pin-prick (performed with a 25 gauge Whitacre needle in the cutaneous distribution of the saphenous nerve on the medial aspect of the blocked leg) to monitor for the duration of the sensory block until sensation is fully returned. This testing will be performed by research assistants. If the duration of their sensory block should last past admission, the patients will be educated during their hospitalization assessments on how to assess their own block every two hours at home using a safety pin. Research assistants will continue to call patient's every two to three hours

during this time until block resolution occurs to instruct the participants and answer any questions. During their stay, their pain management will be managed by the Acute Pain Service. They will also be asked about their pain using the visual analog scale, post operative nausea and vomiting rates, and opioid consumption will be followed. Comparisons will then be made between the three groups and the data will be analyzed.

Outcomes Measures:
Subjects will be evaluated for the efficacy of a sensory blockade on the operative limb. Complete sensory analgesia will be defined as analgesia to pinprick in the distribution of the saphenous nerve. The primary outcome will be time to resolution of the nerve block as assessed by pinprick over the saphenous nerve distribution, secondary outcomes will include but not limited to pain scores, use of post-operative opioids, and the incidence of nausea and vomiting will be recorded over the course of 24-48hrs. Subjects will also be followed to evaluate for potential neurologic complications such as persistent paresthesias in the distribution of the saphenous nerve.

Analytical Plan:
Power / Sample Size:
The primary sample size consideration is the comparison between the 1 mg and 4 mg of dexamethasone arms, where the goal is to demonstrate that the duration of PNB is clinically equivalent between the two arms. Note that this hypothesis, statistically, is reversed from what is usually tested in a superiority trial. We have assumed that clinically equivalent means that the average duration of PNB for 1 mg of dexamethasone is ± 4 hours from the average duration for 4 mg. In other words, the difference in mean duration for the two dexamethasone arms (D) falls on the interval (-4 hrs to 4 hrs). Statistically, a successful trial would then reject the null hypothesis H_0: D< -4 hrs or D> 4hrs. The previously mentioned Toronto study [5] reported a mean duration of analgesia of 25 hours (95% CI: 19.5-27.4) for 25 patients randomized to 8 mg of perineural dexamethasone. While the test of clinical equivalence will be based on the boundary of ± 4 hours, in order to permit power calculations one has to make an assumption about the true difference in mean duration. The most liberal assumption is that there is absolutely no difference in mean duration between the arms (i.e. D=0). To be more conservative, we have assumed that the true mean duration for 4 mg of dexamethasone is ± 1.5 hours from the true mean duration for 8 mg. This assumption implies that a study of 50 participants per group (allowing for 10% drop-out) will have >80% power to declare the two doses as clinically equivalent. Note that this calculation assumes a type 1 error rate of 0.05/3 = 0.1667, as the study has three planned comparisons (two dexamethasone doses versus each other, and then both versus the placebo control). We plan to recruit a reduced sample size for the placebo control arm, as the difference in duration of PNB when compared to both dexamethasone arms is expected to be large. Provided the average duration of PNB is at least 5 hours longer for either dexamethasone arm, we will have >90% power recruiting only 15 subjects (allowing for 10% drop-out) to the placebo control arm. Note that the Toronto study [5] reported an average improvement of 11.8 hours when comparing 8 mg of perineural dexamethasone to their control arm.

Human Subjects Protection:

Subject Recruitment Methods:
Potential study participants will be identified based on the posting of their surgical procedure as undergoing elective robotic medial and/or patellofemoral MAKO partial knee arthroplasty. On the day of surgery all patients undergoing this surgical procedure normally come through the regional anesthesia area of surgical services to receive further anesthetic evaluation, education, and potential regional anesthesia procedures. Once they have been consented by the regional anesthesia team for a peripheral nerve block, all patients, regardless of gender, race or age, who qualify for the study based on inclusion and exclusion criteria will be formally asked to participate in the study at this time. All patient information will be kept confidential both during recruitment and throughout the duration of the study.

Informed Consent:
Written informed consent will be obtained from each subject. It can be obtained by any physician listed as part of the study staff. If possible, patients scheduled for elective robotic medial and/or patellofemoral MAKO partial knee arthroplasty will be seen in the preoperative assessment clinic at North Carolina Baptist Hospital. Otherwise, as is typical for regional anesthesia techniques, the study team will meet the patient in the Regional Anesthesia and Acute Pain Management area. They will be informed of the purpose of the study along with the risks, benefits, and alternatives. Questions will be answered and consent obtained. A copy of the signed informed consent will be placed in the patient's medical record. All subjects may decline participation in the study at any time. Informed consent and all necessary study data will be obtained prior to the administration of any sedative medication.

Confidentiality and Privacy
Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, stored separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed at the earliest opportunity, consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring
The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff.

Reporting of Unanticipated Problems, Adverse Events or Deviations
Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB and sponsor or appropriate government agency if appropriate.

Resources:

1. Bailard NS, Ortiz J, and Flores RA. Additives to local anesthetics for peripheral nerve blocks: evidence, limitations, and recommendations. American Journal of Health-System Pharmacy, 2014; 71: 373-385.

2. Albrecht E, Kern C, Kirkham KR. A systematic review and meta-analysis of perineural dexamethasone for peripheral nerve blocks. Anaesthesia 2015(1); 70: 71-83.

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4. Desmet M, Braems H, Reynovoet M, et al. IV and perineural dexamethasone are equivalent in increasing the analgesic duration of a single-shot interscalene block with ropivacaine for shoulder surgery: a prospective, randomized, placebo-controlled study. British Journal of Anaesthesia 2013; 111(3): 445-452.

5. Abdallah FW, et al. Intravenous dexamethasone and perineural dexamethasone similarly prolong the duration of analgesia after supraclavicular brachial plexus block: A randomized, triple-arm, double-blind, placebo-controlled trial. Regional Anesthesia and Pain Medicine 2015; 40(2): 125-132.

6. Fredrickson MJ, Danesh-Clough TK, White R. Adjuvant dexamethasone for bupivacaine sciatic and ankle blocks: results from 2 randomized placebo-controlled trials. Reg Anesth Pain Med. 2013(4); 38:300–307.

7. De Oliveria GS, et al. Peripheral single dose dexamethasone for post-operative pain: a meta-analysis of randomized control trials. Anesthesiology 2011(9);115: 575-588.

8. Williams BA, Hough KA, Tsui BYK, Ibinson JW, Gold MS, Gebhart GF. Neurotoxicity of Adjuvants used in Perineural Anesthesia and Analgesia in Comparison with Ropivacaine. Regional anesthesia and pain medicine 2011;36(3):225-230.

9. Drager C, Benziger D, Gao F, Berde CB. Prolonged intercostal nerve blockade in sheep using controlled-release of bupivacaine and dexamethasone from polymer microspheres. Anesthesiology 1998 Oct;89(4):969-79.

10. Williams, BA. Schott NJ, Mangione MP, Ibinson JW. Perineural dexamethasone and multimodal analgesia: How much is too much? Anesthesia and Analgesia 2014; 118 (5): 912-914.

Appendix:

1. Data Collection Form
2. Consent Form
3. FDA IND Acknowledge/Exemption 125810