A PROSPECTIVE TRIPLE-MASKED RANDOMIZED CONTROLLED TRIAL MEASURING ANALGESIA DURATION OF DEXAMETHASONE, BUPRENORPHINE, OR CLONIDINE WITH ROPIVACAINE FOR INTERSCALENE NERVE BLOCK

STUDY PROTOCOL

1) **Protocol Title:** A prospective triple-masked randomized controlled trial measuring duration of buprenorphine, dexamethasone, clonidine with ropivacaine for interscalene block
2) **Protocol Version:** 2.0
3) **Protocol Initiated:** June 18th, 2012
4) **Protocol Revision Date:**
5) **Protocol Completed Date:** *pending*
6) **Principal Investigator:** Mindy Seering, MD
7) **Research Team:** Michael Todd, MD; John Laur, MD, MS; Julie Weeks, MPT; Pamela Jacobs, RN; Emine Bayman, Ph.D.; All research team members must be IRB certified.
8) **Study Design:** This is a prospective randomized controlled triple-masked study looking at the duration of nerve block analgesia when using the listed adjuvants plus ropivacaine versus plain ropivacaine alone.
9) **Questions:**
   - **a)** When providing a interscalene nerve block (ISB) for painful shoulder surgery using the following four regimens:
     - **i)** 0.75% plain ropivacaine. The reference comparator.
     - **ii)** A mixture of 0.75% ropivacaine with 300 mcg buprenorphine
     - **iii)** A mixture of 0.75% ropivacaine with 0.1 mcg/kg clonidine
     - **iv)** A mixture of 0.75% ropivacaine with and 8mg dexamethasone
   - **b)** Compared to 0.75% plain ropivacaine, will the adjuvant mixture:
     - **i)** Increase block analgesic duration?

     (Defined as elapsed times from block-needle withdrawal until patient-reported time that they were first aware of painful sensation in the operated region of the limb.)

10) **Hypothesis:**

a) **Null Hypothesis:** Compared to plain ropivacaine, the adjuvant mixture:

   i) Will not increase the nerve block analgesic duration time by 25% or more.

b) **Alternate Hypothesis:** Compared to plain ropivacaine, the adjuvant mixture:

   i) Will increase the nerve block analgesic duration time by 25% or more.

11) Primary Outcome:

a) Our primary outcome is the time from nerve block-needle withdrawal to return of:

   i) Painful perception in the operated upon area of the limb.

b) Block Quality: Achieving an inability to sense cold ice-water in the cutaneous distribution of the brachial plexus trunk distal to the block within 30 minutes will be considered a **successful nerve block** preoperatively. If the patient has an inability to sense cold ice-water in the cutaneous distribution of the brachial plexus trunk distal to the block within 30 minutes will be considered a **successful nerve block** postoperatively. Anything less will be considered a **failed nerve block**.

12) Secondary Outcomes:

i) Return of sensory function in the blocked area of the limb.
ii) Return of motor function in the blocked area of the limb.
iii) Post-op Nausea and vomiting before discharge
iv) Nausea and Vomiting after discharge
v) Changes in Blood Pressure (BP) in the PACU defined as any blood pressure +/- 20% of patient's baseline (either BP on admission if no clinic BP is documented, or most recent clinic BP as documented if that exists)
vi) Changes in Blood Pressure in Second Stage defined as any blood pressure +/- 20% of patient's baseline (either BP on admission if no clinic BP is documented, or most recent clinic BP as documented if that exists)

Motor Block Scale Table

	Scale	
Muscle function level	**Grade**	**Percent of normal**
No evidence of contractility	0	0 %
Slight contractility, no movement	1	10 %
Full range of motion with gravity eliminated	2	25 %
Full range of motion against gravity	3	50 %
Full range of motion against gravity, some resistance	4	75 %
Full range of motion against	5	100 %

gravity, full resistance		

Definitions:

a) Duration of Analgesic Block
- **i)** Time from nerve block-needle withdrawal until the **time reported by the patient** that they first had awareness of painful sensation returning anywhere in the surgically operated upon area of the limb.
- **ii)** Patient will be given a form to write time down as it occurs.
- **iii)** They are expected to write down the date and time (hour and minute) they first perceive pain in the arm anywhere in the surgical area. (even if they wake up from sleep and first notice pain there).
- **iv)** They will be telephoned within three days from the block to gather the data from the patient.
- **v)** If they cannot find the form or did not write the date and time down, we will then use the date and time the patient recalls from memory.

a) Duration of Sensory Block
- **i)** Time from nerve block-needle withdrawal until the **time reported by the patient** that they first had awareness of tactile (light touch) sensation returning anywhere in the blocked area. Patients will be given a form to write time down as it occurs. They are expected to write down the date and time (hour and minute) they first felt sensation return to the blocked area (even if they wake up from sleep and first notice sensation returned).
- **ii)** They will be telephoned within three days from the block to gather the data from the patient.
- **iii)** If they cannot find the form or did not write the date and time down, we will then use the date and time the patient recalls from memory.

a) Approximate Duration of Motor Block
- **i)** Time from nerve block-needle withdrawal until the **time reported by the patient** that, with the arm of the blocked extremity, they are able to **flex their bicep.** Patient will be given a form with a diagram and instruct them prior to sedation and placing the block. They will write the time down when they are able to achieve this outcome. They are to write down the date and time (hour and minute) they were first able to flex their bicep on the blocked limb.
- **ii)** They will be telephoned within three days to gather the time from the form.
- **iii)** If they cannot find the form or did not write the data down, we will then use the time the patient recalls from memory.

a) Patient Satisfaction with the block
- **i)** Patients will be asked the question: "Would you want a nerve block again if you needed a similar surgery in the future?" Yes / No

Secondary Outcomes Table

Did patient have nausea before discharge	
Yes	No
Did patient have vomiting before discharge	
Yes	No
Did patient have nausea after discharge (72 hours)	
Yes	No
Did patient have vomiting after discharge (72 hours)	
Yes	No
Did the patient have +/- 20% deviation of baseline Blood pressure in PACU from admission	
Yes	No
Did the patient have +/- 20% deviation of baseline Blood pressure in Second Stage Recovery from admission	
Yes	No

2) Study Background Information:

Regional anesthesia in the ambulatory surgery center venue has been shown to decrease unwanted side effects of anesthesia and improve patient satisfaction with their operative care. Clinicians often seek ways to increase the duration of peripheral nerve blocks(1, 2) for outpatient surgery. This may enhance patient satisfaction and make for fewer unwanted post-operative side effects from anesthesia such as nausea and vomiting. One way to prolong regional anesthesia for patients is to send them home with a peripheral nerve catheter. (3-6) However, there can be multiple interventions associated with these. Catheter adverse conditions include infection, local anesthetic toxicity, catheter failure or dislodgement, infusion leakage, difficulty for the patient to remove their own catheter, and inadequate access to medical resources(7-9).

Adding adjuvants to local anesthetics has been a principle for some time. Anesthesiologists have been adding epinephrine to spinal Marcaine to extend the spinal duration for years. Candido and Franco both added buprenorphine to upper extremity blocks and received triple the pain relief duration from their nerve blocks(10, 11). In addition Candido also added buprenorphine to a sciatic nerve block and received and additional 6 hours of pain relief(12). Cummings (13)of the Cleveland Clinic studied dexamethasone added to interscalene blocks and showed it added twice as much analgesic duration to the nerve block(14-16). Kim and Movafegh also studied adding decadron to local anesthetics and showed prolongation of sensory and motor block (16-17). Casati's research showed that adding Clonidine to Ropivacaine extended his sciatic femoral nerve block extended his pain relief for 3 hours(17-19). Although neither three adjuvant is FDA approved for perineural applications, they have been used in many studies without any detriment to patients(20). Dr. Brian Williams, of the University of

Pittsburg has extensiveky studied these adjuvants on a laboratory level and has not shown any neural toxicity with these adjuvant additions(21, 22). Steroids have also been used in epidural injections for years without problems. Dexamethasone has even been used (23). Clonidine has been studied for epidural and intrathecal applications(24-26). It is FDA approved for used in epidural with chronic pain patients. Currently, we are using clonidine at the University of Iowa Hospitals and Clinics in our Acute Pain Service. We have it in our epidural solution for pediatric patients. Buprenorphine has also been studied for use intrathecally without problems(27). There is a study by an oral surgery department showing its safety and efficacy when added to oral nerve blocks(28).

Study Methods:

This study will be performed in the Ambulatory Surgery Center at the University of Iowa. All included patients will be undergoing orthopedic surgery on their shoulder for a surgery on the shoulder girdle, excluding the scapula. All regional blocks will be performed or directly observed and guided by the listed investigators. Blocks will be done using the interscalene approach to the brachial plexus. All the injections will be placed using simultaneous ultrasound guidance and a nerve stimulator technique with a previously published compressed air injection technique to limit injection pressure.(29, 30)

Per previous protocols involving anesthesia studies at University of Iowa Hospitals and Clinics (UIHC), those patients who are eligible will be given information on the day of surgery. A nurse <u>not</u> involved with the study will give the patient a card briefly informing the patient that they are eligible for a nerve block study. If the patient indicates their consent to hear more and possibly enroll in the study, a representative from the investigating team will *then* meet with the patient to explain the study and obtain informed consent.

An offer of regional anesthesia with or without intravenous sedation or general anesthesia will be provided to all patients regardless of their decision to participate or not. The techniques, practices, medications and use of ice-water to test blocks described in this protocol are currently used in common practice.

3) Inclusion Criteria:

Patients who have or are:

- **a)** Orthopedics service patients having **shoulder surgery**
- **b)** ASA class I, II, or III.
- **c)** Patients at least 18 years old but less than 71 years old.
- **d)** Patients giving informed consent.

2) Exclusion Criteria:

Patients who have or are:

- **a)** An inability to cooperate during the block placement.
- **b)** Any neuropathy
- **c)** Diabetes
- **d)** Documented kidney disease
- **e)** Documented Hepatic disease

f) A lack of or inability to give informed consent.
g) Currently incarcerated.
h) Pregnancy

3) Consent:

- **a)** The study will be explained to the patient's satisfaction, their questions will be answered, and informed consent will be obtained from the patient after explanation of the risks, benefits, and alternatives.
- **b)** Once the patient has consented to the study, they will be included in the study and followed throughout.
- **c)** Patients with failed blocks will be included in the intention to treat analysis.
- **d)** If the block is unable to be placed due to infection at the site, poor visualization of structures with the ultrasound, inability to obtain study drugs within a reasonable time frame, or unexpected operator difficulty in placing the block, the patient will not be included in the intention to treat analysis and dropped from the study.

4) Randomization:

- **a)** A computerized random number generator will be used by a staff of the Anesthesia Department not involved with the study. They will create a randomized numbered sequence with four groups (A, B, C or D) that will be given to the pharmacy team. This will be used to fill study syringes in the sequence according to the randomization schema.
- **b)** The UIHC Pharmacy will compound the study drugs and will fill and label the coded study syringes.
- **c)** Coded study syringes must be created and delivered within 30 minutes of the physician's request.
- **d)** The Pharmacy will keep a record of which patient received each coded syringe and the solution they contained.
- **e)** They will be given to the practitioner at the time of block placement.
- **f)** Practitioners will perform the block using the pharmacy coded study drug.

5) Masking:

- **a)** Masking will be accomplished by using coded labels on the study mixtures.
- **b)** At the end of the study enrollment, information given to the statistical analyst will be blindly coded as groups A, B, C or D for data analysis.
- **c)** The Pharmacy will keep the group codes until after data analysis is complete.
- **d)** The anesthesiologist and nurse assistants will be masked to the study mixtures.
- **e)** Any assisting anesthesia Staff, Fellows, Residents, CRNAs, SRNAs, or medical students will be masked to the study mixtures.
- **f)** Patients will be masked to the study mixtures.
- **g)** Any person collecting and/or scribing the data will be masked to the study mixtures.
- **h)** Any person analyzing the data will be masked to the study mixtures.
- **i)** Once all the data has been collected and analyzed according to group code, the blinding on the study mixtures can be broken and the codes for the study mixtures made known.
- **j)** Safety monitors will not be masked to the mixtures. They can communicate with the pharmacy to unmask the mixtures for only themselves. They will not report the mixtures or pharmacy codes to anyone except for patient safety purposes.

k) The coded sample syringes will be kept for reanalysis in case there is any question of what mixture was given to any patient. The syringe contents can be tested by the pharmacy and a group code for that patient or set of patients will then be given to the analyst. The masking will remain intact.

6) Study Mixtures

a) The local anesthetic study mixtures volumes will be the same (32mL) and contained in two thirty-milliliter syringes with 16 mL in each. They consist of:

i) 0.75% Ropivacaine x 30mL (225 mg max dose) + 2 mL saline for a total volume of 32 mL

ii) 0.75% Ropivacaine x 30mL (225 mg max dose) with 300 mcg buprenorphine (1 mL) + 1 mL sterile saline for a total volume of 32 mL

iii) 0.75% Ropivacaine x 30mL (225 mg max dose) with 100 mcg/kg clonidine (0.1 mL) + 1.9 mL sterile saline for a total volume of 32 mL

iv) 0.75% Ropivacaine x 30mL (225 mg max dose) with 8mg dexamethasone (2 mL) + 0 mL sterile saline for a total volume of 32 mL.

v) **Note:** *If drug shortages occur during the study and we are unable to use the same concentration of any additive drugs (e.g. dexamethasone 10mg/mL instead of 4mg/mL), then a substitution will be allowed and the total volume in the syringe will be changed so that all syringes will be the same volume and final ropivacaine drug mass.*

7) Techniques:

All the blocks will be performed:

a) Either by, or under the direct supervision and direction of the Primary Investigator or regional anesthesia faculty listed on the investigation team.

b) In the Ambulatory Surgery Center at the University of Iowa Hospitals and Clinics using the posterior approach to the brachial plexus at the trunk level.

c) A timeout will be performed before the block to verify the patient, site of surgery and that we are blocking the correct side (already marked).

d) Using sterile technique, cleaning the skin with tinted chlorhexidine and with the operators wearing caps, masks, and sterile gloves. The ultrasound probe will have a sterile sheath over it. Sterile ultrasound gel will be used.

e) With ultrasound guidance and nerve stimulator from 0.2 mA to 2.0 mA using a sterile Arrow 90mm insulated stimulation needle (StimuQuick).

f) If we are unable to stimulate the brachial plexus at the trunk level with the nerve stimulator, we will place local anesthetic in the region where the brachial plexus nerves are visualized using ultrasound based on the practitioner's experience with ultrasound-guided interscalene (brachial plexus trunks) nerve blocks.

g) Block start and end times will be recorded. Start time begins at block needle insertion. Stop time is the time of nerve block-needle withdrawal.

h) All patients will be monitored with blood pressure, pulse oximetry, ECG and have 2 liters per minute of oxygen administered by nasal cannula.

i) Emergency resuscitation equipment, intralipid, and emergency medications are present and immediately available for patient safety.

j) Anesthesiologists will be present and/or immediately available should resuscitation efforts be necessary in the unlikely event of drug toxicity, cardiac arrest, or other adverse event.
k) Any adverse outcomes (listed in "stopping rules" #23 below) will be reported to the Safety Monitors on the day it happens.
l) The use of rescue blocks in the PACU will be counted and analyzed.

8) Statistics
a) For our **primary outcome**, we will use ANOVA or Kruskall-Wallis test, after checking the normality of the data, to compare the duration of the analgesic block. If we find a difference among all 4 groups, we will use 2-sample t-test or Mann-Whitney U-test to explore differences between the individual groups.
b) For our continuously distributed **secondary outcomes**, given that outcomes will be observed on every patient, we will use ANOVA or Kruskall-Wallis test. For outcomes with categories (nausea and vomiting and blood pressure), we will use the chi-square test. Similarly, we will explore the different group or groups using chi-square test or Fisher's Exact test.
c) We based our estimates upon Cumming's, Candido's and Casati's previous studies and our clinical experience. We have estimated the expected additional analgesic time between the three groups.
d) Using the above parameters, a sample size is 40 per group with 4 total groups calculates to a sum of 160 subjects while using 90% power and 0.05 type I error rate.

9) Safety Monitoring:
a) An Anesthesiology Faculty member who is not involved in the study will act as safety monitor and will review the data and any complications when half of the patients (n = 80) have been completed.

10) Stopping Rules:
a) Any incidence of patient complications that occur with an incidence higher than published data for the following complications for peripheral nerve blocks will be enough cause for the Safety Monitors to stop the study(31, 32). Numbers in parentheses below are the highest incidence reported in the referenced article for peripheral nerve block complications. The highest incidence of complications was reported to be from the supraclavicular block, which we will not be performing. We are relying on results reported from our own regional anesthesia follow-up clinic. This is a clinic developed here to see patients with troublesome complications of peripheral nerve blocks. The complication rates have been reviewed and studied since the clinic inception over 4 years ago(33). We are erring on the side of caution by using higher complication rates of the supraclavicular adverse event reports.

b) Published Peripheral Nerve Block Complication rates:
i) Seizure (26.3/10,000)
ii) Cardiac arrest (Code Blue) (15.9/10,000)

iii) Respiratory Failure (15.9/10,000)
iv) Peripheral neuropathy (32/10,000)
v) Patient death (15.9/10,000)

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