Double Blinded Randomized Controlled Study Evaluating the Analgesic Duration of Dexmedetomidine compared to Dexamethasone as adjuncts to Single Shot Interscalene Block in Patients Undergoing Ambulatory Shoulder Surgery

Introduction:

With the rapidly increasing proportion of surgeries being performed in an ambulatory setting, there is a significantinterest in post-operative outpatient analgesic strategies.Regional anesthesia is often the most efficient and safe modality for controlling pain, as well as decreasing length of hospital stay, reducing common side effects of opioid centered analgesia, and improving overall patient satisfaction. Particularly in shoulder surgery, postoperative pain poses a challenge to both the anesthesiologist and orthopedic surgeons. In an effort to improve analgesia and facilitate mobilization, regional anesthesia in the form of an interscalene approach to the brachial plexus is often used, either as the primary anesthetic or as an adjunct to general anesthesia. Peripheral nerve blockade can often be a deciding factor tipping the scales on how well patients tolerate the initial recovery period.Pain control at time of discharge and in the initial 24-48 hours after surgery can result in decreased opioid consumption, decreased opioid related side effects, and reduced rate of hospital re-admission secondary to pain.

The addition of various adjuvants to local anesthetics is a common practice in modern regional anesthesia. There have been many attempts to identify adjuncts in peripheral nerve blockade that can increase the duration of analgesia, are easy to administer, and simultaneously maintain a safe side effect profile. Currently, the most commonly employed adjunct to peripheral nerve blockade is perineural dexamethasone. In general, at the doses used in regional anesthesia, dexamethasone has a minimal side effect profile. However, while it has been shown to increase duration of analgesia, there have been concerns regarding its neurotoxicity in animal studies. In addition, dexamethasone has the potential to cause hyperglycemia in patients with impaired glucose metabolism as well as perineal pain and pruritis when administered peripherally.

Dexmedetomidine is a highly selective alpha-2 agonist that is commonly used in patients undergoing anesthesia or requiring sedation in a non-operative setting. As a peripherally administered medication, it has both sedating and analgesic properties, as well as the added IRB NUMBER: 2015-5628 IRB APPROVAL DATE: 01/14/2016 benefit of avoidance of respiratory depression. Although it can rarely produce cardiac depression at high doses, its side effect profile is otherwise minimal and is generally very well tolerated by most patients. When administered peripherally, dexmedetomidine has most commonly been associated with side effects such as hypotension, respiratory depression, and bradycardia – although all at significantly higher doses than planned in our study.The safe use of perineural dexmedetomidine together with local anesthetics hasbeen described on numerous occasions. Nevertheless, although it has been shown to potentiate peripheral nerve blockade and prolong duration of analgesiain various studies (2, 5, 6), it remains rarely used as an adjunct to regional anesthesia.

The purpose of the study we are proposing is to determine if perineural dexmedetomidine can provideincreasedprolongation of analgesia when compared to perineuraldexamethasonein patients

receiving regional block for shoulder surgery. If so, dexmedetomidine may serve as a superior adjunct to peripheral nerve blocks in a rapidly evolving, ambulatory-centered surgical setting.

Hypothesis:

The mean 24 hour opioid usage will be different in one of the three groups.

Primary Objective:

Opioid requirements at 24 hours (morphine equivalents) in patientsreceivingupper extremity nerve block for ambulatory shoulder surgery.

Secondary Endpoints:

48-hour opioid requirements (morphine equivalents)

Time to discharge from PACU Time to first opioid consumption (Patients will be asked to document exact times)

Return of motor and sensory function – questionnaire administered via post-op phone call (Patients will receive copy of questionnaire and will be asked to document exact times)

Side effects encountered

Design and methods:

This is a randomized controlled, double blind studyin patients receiving regional nerve blocksfor upper extremity surgeries in an ambulatory surgical setting. At our surgical center, majority of patientsundergoingupper extremity peripheral nerve block currently receive a combination of local anesthetic and dexamethasone. For this study, patients will be randomized into three groups. All groups will undergo single shot peripheral never block for their upper extremity surgery. One group will receive dexmedetomidine as an adjuvant to local anesthetic, a second group given dexamethasone as an adjuvant, and a third group given no adjuvant to serve as the control.

Inclusion Criteria:

- ASA 1 and 2
- 18-65 years old

- Patients scheduled for ambulatory arthroscopic or open surgery

Exclusion Criteria:

- ASA 3 and 4
- Pre-existing pain disorder
- Regular consumption of chronic pain medication
- Anatomical abnormalities of upper extremity
- Know allergy or hypersensitivity to Ropivacaine or other amide local anesthetics
- Know allergy to dexmedetomidine
- Coagulopathy
- Uncontrolled diabetes

At our institution, shoulder surgery is performed under general anesthesia with interscalene brachial plexus block as a modality for intraoperative and post-operative pain control. Although patients often do receive opioids during induction of anesthesia for airway instrumentation, intraoperative analgesia relies mainly on peripheral nerve blockade – often with minimal or no additional opioid administration.

As a routine standard of practice in our institution, the regional clinical care member calls the patient the evening before and explains the procedure and conducts the pre-anesthesia evaluations. During this phone call, the study will be presented to the subject and if the subject is interested one of the research members listed on the protocol will explain the study in detail and will obtain a verbal consent. On the day of the surgery, one of the research members will meet agreed patients (phone consent) at the registration and will explain the study once more before obtaining the signatures on the IRB approved informed consent.

Because this study aims to evaluate a subjective endpoint like pain, all potential participants will initially undergo a Short Form of the Fear of Pain Questionnaire to improve the uniformity of the study population. The questionnaire consists of nine specific scenarios associated with pain that are graded by participants on a scale of 1(no pain at all) to 5 (extreme pain). All consented patients will fill out the Short Form of the Fear of Pain Questionnaire.

On the day of surgery patients will arrive at the surgical center and undergo pre-surgical evaluation by the anesthetic team. After obtaining consent and completing all necessary paperwork, they will be taken to the post anesthesia care unit where our pre-operative nerve blocks are typically performed. Under standard monitors study participants will undergo preIRB NUMBER: 2015-5628 IRB APPROVAL DATE: 01/14/2016 operative single shot interscalene nerve block under ultrasound guidance and peripheral nerve stimulation. Patients will be randomly assigned to receive on of three injections:

1. Ropivacaine 0.5% 20ml (acting as control)

2. Ropivacaine 0.5% 20ml + 4mg dexamethasone

3. Ropivacaine 0.5% 20ml + 75mcg of dexmedetomidine

Although no official consensus has been reached, 4mg-8mg of perineural dexamethasone in peripheral nerve block is accepted as a safe and effective dose in most current practice.Dexmedetomidine has been administered perineurally in doses ranging from 20- 100mcg. The above dose was chosen for our study arbitrarily as one that has been both beneficial and devoid of significant side effects in current literature. Local anesthetic and adjunct will be drawn up by a physician or nurse not directly involved in patient care. The contents of solution will remain unknown to both the patient and physician performing the nerve block.

Participants will undergo motor and sensory assessment immediately postoperatively in the PACU. This will be done to confirm effective interscalene nerve block. Although we do not anticipate a significant number of failed nerve blocks, patients with failed block – either by motor and sensory evaluation or by the need for significant opioid administration intraoperatively - will be excluded from further follow up.

Outcomes and Post-Operative Follow-up:

Study participants will receive a printed questionnaire upon enrollment and asked to note several events over the 24-48 hours after surgery.

1. Time of return of sensation in shoulder/arm

2. Time of return of motor function – ability to abduct shoulder IRB NUMBER: 2015-5628 IRB APPROVAL DATE: 01/14/2016

3. Time of first sensation of pain

4. Type and dose of oral pain medication prescribed

5. Time of first dose of oral pain medication

6. Total medication taken at 24 hours after surgery

7. Total medication taken at 48 hours after surgery

8. Overall satisfaction with having peripheral nerve block for pain control (1 – unsatisfied, 2 – somewhat satisfied, 3 – satisfied, 4 – very satisfied, 5 – extremely satisfied).

After documentation of time to discharge from PACU, all other endpoints will be obtained via follow up phone call at 24 and 48 hours after surgery. Because of variability in type and dose of oral pain medication prescribed by different surgeons, all opioid consumption with be converted to morphine equivalents.

At our institution it is routine standard of care for patients to receive a post surgical follow up phone call from the nursing staff to assess general recovery. The additional questions described above are different from the typical follow up and will be carried out by an anesthesiologist involved in the study.

Randomization:

Once patients meet all inclusion criteria, they will be randomly assigned to receive one of three interscalene injections (ropivacaine 0.5%, ropivacaine 0.5% + dexamethasone 4mg, or ropivacaine 0.5% + dexmedetomidine75mcg).

Subjects will be randomized on the day of the procedure.Simple randomization will be used to assign patients into one of the three groups. Pre sealed randomization envelopes will be opened just before performing the block. A physician or nurse that are not part of data collection and not directly involved in the care of the patient will be provided with a sealed envelope corresponding to each respective group with instructions on which medication to prepare for the nerve block injection. The medication syringe will be labeled only with a numerical randomization code and IRB NUMBER: 2015-5628 IRB APPROVAL DATE: 01/14/2016 handed to the physician performing the nerve block just prior to injection. A faculty member not directly involved in the study or in patient care will hold all randomization codes.

Unblinding:

In general, unblinding of study treatments during a clinical trial is not allowed unless there are compelling medical or safety reasons to break the blind treatment code, such as in a condition needed to treat serious adverse effects. In case of emergency, if it is necessary to break the blind, the principal investigator or his designee will be able to obtain the randomization key. The IRB andDSMB will be notified and the date, time and reason for unblinding will be recorded.

Statistical Analysis:

Primary objective of the study is to compare the amount of 24 hours opioids (opioid equivalence) used by the three groups. Our own clinical audit and published literature reported 50mg ±20mg of opioids in the first 24 hours. The study is powered to demonstrate a 20% difference between the Dexamethasone group and 30% difference between the placebo group. Based on a two-sided alpha of 0.05 and Type II error of 20% to achieve a clinically significant 30% difference a total of 105 subjects needed to be studied. Sample size calculation is based on the hypothesis that, in one of the groups the mean 24 hours opioid usage will be different.

Primary endpoint of the study, 24 hour opioid requirements is a continuous variable, depending on the distribution of the data, parametric one-way ANOVA or a non-parametric Kruskal Wallis test will be used

for analysis. For all the secondary outcomes time in minutes will be calculated from end of anesthesia time to the events mentioned on the outcomes and post-operative follow up section. Time in minutes is a continues variable, and will be analyzed in a similar way as the primary endpoint. Additionally, if there are covariates that are clinically and statistically different between the groups, data will be analyzed using linear regression analysis and these covariates will be adjusted in the analysis.

Data Management:

All information and patient follow up will be entered into a computer database to be maintained by the principal investigator or their designee. Information in the database will be tracked by the specific randomization code assigned to each patient, which ultimately corresponds to a particular arm of the study

Risks and Benefits:

Both dexamethasone and dexmedetomidine have been used in peripheral nerve blockade in prior studies without any significant side effect experienced by patients. At the doses administered perineurally, the potential risks of the medications are extremely low. As with any peripheral nerve block, potential complications such as nerve damage, bleeding, infection, damage to surrounding structures, and seizure are all potentially possible. However, with the use of ultrasound guidance, peripheral nerve stimulation, and experienced providers, the overall risk of the procedure and the proposed study remains very low.

Data Safety Monitoring Plan:

All the serious adverse events will be reported to the DSMB and the continuation of the study will be at the discretion of the DSMB and the IRB. The DSMB should meet every 6 months to review the status of the research in addition to when a serious adverse event occurs.

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