Prospective Randomized Control Trail Evaluating Single Shot Exparel versus Indwelling Interscalene Catheter for Total Shoulder Replacements- A Pilot Study

Introduction:

Shoulder surgery, especially shoulder replacement surgery, is well known to involve severe postoperative pain. Regional anesthesia is often the most effective and safe modality for pain control, decreasing opioid consumption and its associated side effects and allowing for earlier rehabilitation necessary for improving shoulder surgery outcomes. (1, 2) Better analgesia, therefore, can reduce hospital length of stay, decrease costs, and improve overall patient satisfaction. For major shoulder surgeries, the interscalene nerve block is a well-recognized and efficient procedure for controlling pain. Having a continuous infusion of local anesthetics through an indwelling interscalene catheter is the best technique for pain control after shoulder surgery. (1) Our standard of care for total shoulder replacement surgeries involves placement of an indwelling interscalene catheter that is attached to an On-Q pump, which infuses a low dose local anesthetic at a set rate continuously until the catheter is removed usually on a postoperative day 2. The continuous infusion of local anesthetic through an indwelling catheter allows for a more prolonged nerve block and analgesia as compared to a single shot interscalene nerve block, whose analgesic duration depends on the local anesthetic and any additives given at the time of the block.

While placing an indwelling nerve catheter can prolong pain control, it can also have drawbacks and complications. While major complications like pneumothorax and hemidiaphragmatic paresis from interscalene continuous peripheral nerve blocks (CPNB) are rare, minor adverse effects associated with CPNBs may be more common. They include infection and anatomical damage to blood vessels and nerves due to the indwelling catheter. (3) In addition, catheters take a significantly longer time to set up and place than single shot blocks, which is important as there is often a rush to block patients and trying to get them into the operating room on time. Furthermore, the needle used for catheter placement is larger than the single shot needles, which creates more discomfort to patients during the nerve block. The catheter itself is taped around the entire sides and back of the patient's neck, which is also uncomfortable for patients. Because of how shallow the interscalene block is, the catheter is often found to be dislodged from operating room positioning, patient transport or movement, which negates the placement of the catheter. An indwelling catheter must also be followed up by the acute pain service team until the catheter is removed.

Exparel, or liposomal bupivacaine, is formulated to release low dose bupivacaine over 96 hours, and was recently approved by the FDA in April 2018 to be used in interscalene blocks. The sustained release of local anesthetic could theoretically act similarly to the continuous infusion of local anesthetic through an indwelling interscalene catheter, and could thus avoid the need for placement of a catheter. Current existing data, although inconclusive, has in some studies shown an equal analgesic effect as catheters. (4) As per pharmacy, the cost of the On-Q pump and the

local anesthesia needed for the pump together cost $390 for each indwelling catheter placed, not including the cost of anesthesia and pharmacy supplies and labor. The cost of each 20 mL vial of Exparel is less at $285 and, for a single shot nerve block, would avoid the extra costs and time needed for a catheter placement.

We would like to perform a prospective randomized controlled pilot study to examine the efficacy of single shot interscalene blocks using Exparel versus the traditional interscalene catheter used at our institution. The purpose of the study we are proposing is to determine if single shot interscalene nerve blocks using Exparel can provide equivalent or better analgesia than indwelling interscalene catheter in patients who undergo total shoulder replacement surgery. If so, single shot interscalene nerve blocks with Exparel may serve as a quicker, easier, cheaper, safer, and more comfortable alternative to placing indwelling interscalene catheters.

Hypothesis:

Single shot interscalene nerve blocks using liposomal bupivacaine provides superior analgesia than indwelling interscalene catheters for total shoulder replacements.

Primary Objective:

Patient opioid requirements at 24 hours in morphine equivalents

Secondary Endpoints:

-Intra-operative opioid requirements (morphine equivalents)
- 48-hour opioid requirements (morphine equivalents)
-Patient pain scores in the PACU

Tertiary Endpoint:

-Hospital length of stay

Design and Methods:

This is a randomized controlled study in patients undergoing total shoulder replacement surgery. At our institution, these patients typically receive an indwelling interscalene catheter and undergo general anesthesia for the surgery. For this study, patients will be randomized into two groups: group 1 will receive an indwelling interscalene catheter, while group 2 will receive a single shot interscalene nerve block with liposomal bupivacaine.

Group 1 will receive an indwelling interscalene catheter placed posterior to C5-C6 nerve roots, and given 15 mL of 0.5% ropivacaine plain for the block with no superficial cervical block. The

On-Q pump will be set at a rate of 4 mL/hr. A maximum sedation of 2mg of midazolam and 100mcg of fentanyl may be used for the block.

Group 2 will receive a single shot interscalene nerve block using 20 mL of a mixture of 10 mL of Exparel and ten mL of 0.5% bupivacaine. A maximum sedation of 2mg of midazolam and 100mcg of fentanyl may be used for the block.

All nerve blocks and catheter placements will be performed under ultrasound guidance with an in-plane technique using a stimiplex needle, without twitch monitor, by a trained expert in the regional anesthesiology division. The study medications will be drawn up by the regional anesthesiologist performing the block.

All patients will undergo general anesthesia and receive the same intraoperative and postoperative analgesic regimen. Intraoperatively, patients may receive 100mcg of fentanyl for induction, 0.35mg/kg of ketamine before incision, 1g of IV acetaminophen if no contraindication and maximum of 2mg of hydromorphone. Postoperatively, patients will receive a hydromorphone PCA set at 0.2mg with a lockout of 6 min and no basal dose. Patients will also be ordered for 650mg acetaminophen every 6 hrs standing if no contraindication. To clarify, the study procedure will be done in addition to standard of care.

The consents will be available and given to patients by IRB approved personnel when they come in for their pre-op evaluation visit. Key personnel will explain the study to patients then. If patients would like more time to decide, they make take the consent home with them and have until day of surgery to sign and agree.

Inclusion Criteria:

- ASA 1, 2, and 3
- Ages 40-74
- Patients scheduled for total shoulder replacement

Exclusion Criteria:

- ASA 4 and 5
- Pre-existing pain disorder
- Regular consumption of chronic pain medication
- pregnant women
- any medical condition such as a clotting disorder
- anatomic abnormality that precludes use of an indwelling scalene catheter
- BMI >40
- Patient refusal
- Pre-existing diabetic neuropathy or Hemoglobin A1c >9
- Failed block

Randomization:

Subjects will be randomized on the day of the procedure. A 1:1 random allocation sequence will be used to assign patients to one of the two groups. Pre-sealed randomization envelopes will be opened just before performing the block. A physician or nurse that is not part of data collection and not directly involved in the care of the patient will prepare the drug according to the randomization allocation. A faculty member not directly involved in the study or patient care will maintain the randomization codes.

In case of emergency, the principal investigator or his designee will be able to obtain the randomization key. The IRB and DSMB will be notified of the date, time and reason for obtaining randomization key will be recorded

Statistical Analysis:

In this hypothesis-generating pilot study, we are assuming a large effect size between the groups. In our clinical audit, the average amount of opioid used by these patients is 29 $\pm$ 12 mg. For the sample size calculation, we are expecting a 50% difference in opioid consumption between the two groups. Based on a two-sided alpha of 0.05 and Type II error of 20% to achieve a clinically significant 50 % difference a total of 24 subjects needed to be studied. In order to accommodate the missing cases, we are increasing the sample size to 14 patients per group.

The primary endpoint of the study, 24-hour opioid requirements is a continuous variable a non-parametric Wilcoxon rank sum test will be used for the analysis. For all the secondary outcomes continues variable, will be analyzed similarly as the primary endpoint and categorical variables will be analyzed using chi-square analysis or Fischer's exact test. All the outcomes will be reported with 95% confidence interval. For all analysis, a p-value of 0.05 is considered as statistically significant. There will be no interim analysis for this study. As this is a hypothesis-generating study with small sample size, all the analysis will be reported as unadjusted.

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:

Exparel is a sustained-release formulation of bupivacaine and thus has similar safety profile as other local anesthetics commonly used for peripheral nerve blockade. It has been used in other peripheral nerve blockade without any significant side effect experienced by patients. As with any nerve block, potential complications including bleeding, infection, nerve damage and

damage to surrounding structures, and seizures may occur. However, with the use of ultrasound guidance by experienced providers, the overall risk of the procedure and the proposed study remains very low. (5, 6) On the other side, the indwelling catheter also has risks such as infection and anatomical damage to blood vessels and nerves.

Data Safety Monitoring Board:

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.The DSMB will consist of Dr. Naum Shaparin and Dr.John Pope

References:

1. Borgeat, Alain, and Georgios Ekatodramis. "Anaesthesia for shoulder surgery." *Best Practice & Research Clinical Anaesthesiology* 16.2 (2002): 211-225.
2. Dowell, Deborah, Tamara M. Haegerich, and Roger Chou. "CDC guideline for prescribing opioids for chronic pain—United States, 2016." *Jama* 315.15 (2016): 1624-1645.
3. Wiegel, Martin, et al. "Complications and adverse effects associated with continuous peripheral nerve blocks in orthopedic patients." *Anesthesia & Analgesia* 104.6 (2007): 1578-1582.
4. Sabesan, Vani J., et al. "A prospective randomized trial to identify the optimal postoperative pain management in shoulder arthroplasty: liposomal bupivacaine vs. continuous peripheral nerve block." *Journal of Shoulder and Elbow Surgery* 26.5 (2017): e150.
5. Ilfeld, Brian M., et al. "Safety and side effect profile of liposome bupivacaine (Exparel) in peripheral nerve blocks." *Regional anesthesia and pain medicine* 40.5 (2015): 572-582.
6. Richard, Brigitte M., et al. "The safety of EXPAREL®(bupivacaine liposome injectable suspension) administered by peripheral nerve block in rabbits and dogs." *Journal of drug delivery* 2012 (2012).