NCT03496610

- **Study Title:**

Intraoperative surgical wound infiltration vs Quadratus Lumborum (QL) Block for post-operative pain control after nephrectomy in living donor kidney transplant patients.

- **Short Title:**

Surgeon infiltration QL block comparison

- **Research Abstract:**

The purpose of this study is to determine whether there is a difference between surgical site infiltration of local anesthetic versus ultrasound-guided truncal block (Quadratus Lumborum, QL block).Current practice at Duke is to infiltrate local anesthetic at the end of surgery by the surgical team or request a member of the regional anesthesia division to provide a QL block.
Given that the administration of a QL block utilizes ultrasound to target a specific anatomical plane where the nerves providing sensation to the abdominal wall travel, we hypothesize that this approach will provide superior analgesia and improved morbidity when compared to direct injection of local anesthetic to the wound site.
We will utilize patients undergoing living donor nephrectomies since these are heavily screened and understood to be in excellent health thus eliminating potential confounding variables. These patients will be followed for 7 days after surgery and data will be collected pertaining to their total opioid consumption, pain scores, GI complications, and ability to return to normal pre-surgery physical function levels.
Both parametric and non-parametric data will be analyzed with the appropriate statistical tests. Patients risks will be the same as for patients undergoing donor nephrectomy who are not participating in the study.

- **Primary Objectives:**

The purpose of this study is to determine whether there is a difference between surgical site infiltration of local anesthetic versus ultrasound-guided truncal block (Quadratus Lumborum, QL block). Specifically comparing total 24h opioid consumption.

- **Secondary Objectives:**

The exploratory objectives are:
- Pain scores at which other time points post surgery- hourly for the first four hours, at 6 hours, 12 hours, 24 hours, and
- GI complications (bloating, nausea/vomiting, constipation)
- Total use of PRN pain medication for a total of 7 days post surgery.

- **Purpose of the Study:**

The purpose of this study is to determine whether there is a difference between surgical site infiltration of local anesthetic versus ultrasound-guided truncal block (Quadratus Lumborum, QL block)
we hypothesize that this approach will provide superior analgesia and improved morbidity when compared to direct injection of local anesthetic to the wound site.

- **Background & Significance:**

In 2014 in the United States there were approximately 17,107 kidney transplants performed (https://www.kidney.org/news/newsroom/factsheets/Organ-Donation-and-Transplantation-Stats). Of these a portion, approximately 6,000, were from living donors. Currently there is no consensus on the perioperative pain management strategies for these patients. Given the recent national attention to the ongoing opioid epidemic it seems appropriate to develop non-opioid pain management alternatives. Such strategies have been shown to decrease hospital stay and reduce morbidity associated with opioid use such as nausea and vomiting. Use of local anesthetics during surgery is a strategy currently utilized to reduce opioid use. In this study we aim at answering the question of whether direct wound infiltration of local anesthetic by the surgeon in the field is as effective as U/S guided Quadratus Lumborum regional block.

The Quadraus Lumborum block was described by Blanco *et. Al.* [1] as a way to provide analgesia to truncal/intraabdominal procedures. Relatively recent case reports and studies have shown it to be an effective post-operative analgesic option for abdominal surgery [2-4]. Patients undergoing donor nephrectomies here at Duke Medical Center are already receiving liposomal bupivacaine infiltration by the surgeon or QL blocks with liposomal bupivacaine placed by members of the regional anesthesia team .This study will simply utilize the already existing infrastructure to formally investigate if one technique provides better pain control. We hypothesize the ultrasound guided QL block with liposomal bupivacaine will offer superior post-operative analgesia than surgical field wound infiltration, using decreased 24-h post operative opioid totals. Additionally, as secondary endpoints we will also be examining differences in numerical pain scores post-operatively, GI complications (bloating, nausea/vomiting, constipation) as well as improved functionality of basic motor activities such as walking.

Ultimately, we feel that those patients who stand to gain the most benefit from this new intervention will be the kidney transplant recipients. However, given that this population tends to have high co-morbidities, which may confound our findings, we have elected to initially carry out this study on living kidney donors. These patients undergo rigorous selection and are thus a population with low to no co-morbidities and in generally healthy state. Such a population would be ideal to elucidate differences between pain control strategies where the impact of confounding variables would be minimized.

In summary we believe this study will help develop an important strategy aimed at post-operative pain control. Additionally, this study will help the continued development of non-opioid alternatives to pain control and therefore reduce the overall opioid exposure of these patients during the perioperative period.

1. 271: Tap block under ultrasound guidance: the description of a 'no pops' technique. *Regional Anesthesia and Pain Medicine* 32, 130–130 (2007).
2. Murouchi, T., Iwasaki, S. & Yamakage, M. Quadratus Lumborum Block. *Regional Anesthesia and Pain Medicine* 41, 146–150 (2016).

3. Kadam, V. R. Ultrasound-guided quadratus lumborum block as a postoperative analgesic technique for laparotomy. *J Anaesthesiol Clin Pharmacol* 29, 550–552 (2013).
4. Öksüz, G. *et al.* Quadratus Lumborum Block Versus Transversus Abdominis Plane Block in Children Undergoing Low Abdominal Surgery: A Randomized Controlled Trial. *Regional Anesthesia and Pain Medicine* 42, 674–679 (2017).

- **Design & Procedures:**

Preoperatively, patients will be given standard of care premedication: 975mg acetaminophen, 600mg gabapentin, and 80 mg Aprepitant by mouth prior to surgery. These medications may be altered or not given depending on patient comorbidities or other extenuating factors such as allergy/intolerance. Prior to surgery the patients will be randomized to receive either surgical infiltration or QL block. This randomization will be done utilizing an online research randomizer (https://www.randomizer.org/).

Intraoperatively, patients will be given general anesthesia with endotracheal intubation which is the standard of care for these types of procedures. Induction will be achieved with propofol, lidocaine, fentanyl and a non-depolarizing neuromuscular blocking agent. Maintenance will be achieved with sevoflurane. A total of 100 mcg of fentanyl will be given during the case, 25mcg at induction and 75mcg in incremental doses throughout the case at the discretion of the attending anesthesiologist. A one-time IV bolus of 10mg IV dexamethasone (will not be given in diabetic patients) will be administered at the beginning of the procedure. After the completion of the surgery the patient will either receive 266 mg of liposomal bupivacaine mixed with 50 mg non-liposomal bupivacaine infiltrated into the wound by the surgeon or they will get bilateral ultrasound guided Quadratus Lumborum blocks by the anesthesia team. At the conclusion of the case, full neuromuscular reversal will be given, patient will be extubated, and taken to the post-operative care unit (PACU).

Post operatively patients will receive Tylenol 650 mg PO Q6h, Gabapentin 100 mg PO Q8h, and Toradol 15 mg IV Q8h (for a total of 3 doses). Additionally, patients will have post-operative orders for supplementary pain control that include 25mcg IV fentanyl for breakthrough pain, Tramadol 25 mg PO Q6h for pain score of 4-6/10, and Tramadol 50 mg PO Q6h for pain scores 7-10/10.

Upon arriving to the PACU patients will be assessed to determine their level of pain as well as nausea/vomiting. Subjects' verbal pain scores (NRS 11), opioid consumption, and GI complications will be recorded hourly for the first four hours, at 6 hours, 12 hours, 24 hours, and 36 hours post-surgical intervention. 24h opioid consumption (IV morphine equivalents) will be calculated. On post op day 1 patients will be asked to ambulate a short distance of 50ft and we will record pain levels using the numerical pain score reported during this activity. After leaving the hospital patients will be contacted via telephone daily until post op day 7 and will be asked the same questions they were asked during their hospital stay to asses opioid consumption, nausea/vomiting events, and GI complications.

- **Selection of Subjects:**

ASA 1-2 patients aged 18-75 years old undergoing living donor nephrectomy will be enrolled. Patients will be identified in conjunction with the transplant service and will be first contacted by telephone by the primary investigator to determine eligibility and interest. If patients are interested in participating, the study will again be explained on admission to hospital and written informed consent will be obtained the day of surgery prior to receiving any sedation.

Inclusion

Patients that will be included in the study are English speaking 18-75-year-old ASA 1-2 patients undergoing living donor nephrectomy.

Exclusion

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

1) ASA 3 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 standard of care day-of surgery urine 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.

- **Subject Recruitment and Compensation:**

Only patients who are having living donor nephrectomies are eligible for this study. We will not bias any demographic groups in identifying patients eligible for this study. A total of up to 50 patients will be consented from Duke University Medical Center. Patients will not receive any additional compensation for enrollment in this study.

Recruitment will be facilitated by use of Duke "My Chart." A recruitment letter will be sent to potential subjects on behalf of their anesthesia provider informing them of the study with the research team's contact phone number and email address which includes an opt-out option. Research team members will follow up 1 week after MyChart letters/communication have been sent if there has been no response from potential candidates. Written consent will be collected at in-person visit before surgery.

- **Consent Process:**
    - Who will conduct the consent process with prospective participants?
        - PI, sub-Is

- Who will provide consent or permission
  - Participant ONLY (No LAR or parent/legal guardian)
- How much time will the prospective participant have between being approached about participating in the study and needing to decide whether or not to participate?
  - Research team will send "My Chart" message informing potential participant about the study with an option to opt-out or express interest. The patient will then be contacted via telephone or email to schedule the study session date, and will have an opportunity to ask questions at that time. The patient will then have additional time to consider participation prior to arriving for the session
  - In cases where it is not possible to obtain consent the evening prior we would obtain consent the day of surgery. Given that the intervention we are proposing is already happening as part of the routine care, we believe that there is no significant additional risk to the patient and would not be unreasonable to ask for consent the day of surgery if we were unable to obtain it the evening before.
- Where will the consent process occur?
  - It will occur at one of the following places:
    - Surgeon's clinic
    - Pre-operative Clinic
    - In the Preoperative are the day of surgery
- What steps will be taken in that location to protect the privacy of the prospective participant?
  - Throughout the consent process, measures will be taken to maintain privacy, such as conducting face-to-face conversations in private rooms.
- How much time will be allocated for conducting the initial consent discussion, including presenting the information in the consent document and answering questions, with each prospective participant?
  - As much time as necessary will be spent with each potential participant to sufficiently explain and answer all questions, and address all concerns they may have in regard to the study and/or consent process.
- What arrangements will be in place for answering participant questions before and after the consent is signed?
  - Each potential participant will have ample time to ask questions both before and after the consent is signed. The participant will be given a copy of the signed consent with contact information for the PI and may contact the study team to ask additional questions after the session has concluded.
- Describe the steps taken to minimize the possibility of coercion or undue influence?
  - Healthy volunteers will not be recruited from vulnerable populations, including any DUHS students or employees whom members of the study team may have a supervisory role over.
- What provisions will be in place to obtain consent from participants who do not read, are blind or do not read/understand English?
  - Volunteers that are illiterate, blind, or do not understand English will not be eligible for this study.
- Do you plan to obtain written consent for the conduct of research?

- Yes

- **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.

- **Study Interventions:**

After the completion of the surgery the patient will either receive 266 mg of liposomal bupivacaine mixed with 50 mg non-liposomal bupivacaine infiltrated into the wound by the surgeon or they will get bilateral ultrasound guided Quadratus Lumborum blocks by the anesthesia team. At the conclusion of the case, full neuromuscular reversal will be given, patient will be extubated, and taken to the post-operative care unit (PACU).

- **Risk/Benefit Assessment:**

Risks of this study includes the following:

- Risks of Bupivacaine Liposome Given as a Nerve Block:
    - Greater than or Equal to 10% (Common):
        - Nausea, fever, constipation
    - At Least 2% but Less than 10% (Uncmmon):
        - Muscle twitching, taste disturbance, urinary retention, fatigue, headache, confusion, low blood pressure, high blood pressure, itching, sweating, rapid heart rate, anxiety, fall, temporary swelling, sensory loss, change in liver function tests, hiccups, respiratory depression, bruising
    - Less than 2% (Rare):
        - Arrhythmia, slow heart rate, impaired hearing, blurred vision, chills, skin infection, lung/respiratory infection, wound secretion, white blood cell count increase, joint pain and swelling, back pain ,decreased mobility, muscle spasms, muscle weakness or pain, tingling, fainting, sedation, delirium, urinary incontinence, cough, difficulty breathing, blister, redness, rash, bruising, blood clots in extremities, decreased blood pressure when standing
- Risks of Bupivacaine Liposome Given Directly Into the Surgical Wound:
    - Greater than or Equal to 10% (Common):
        - Nausea, constipation, vomiting
    - At Least 2% but Less than 10% (Uncommon):
        - Fever, dizziness, temporary swelling, anemia, low blood pressure, itching, rapid heart rate, headache, insomnia, muscle spasms, back pain, tiredness
    - Less than 2% (Rare):

- Chills, redness, slow heart rate, anxiety, urinary retention, tremor, dizziness when standing, tingling, fainting, high blood pressure, muscle weakness, neck pain, rash, sweating, arrhythmias, confusion, mood changes, respiratory depression, urinary incontinence, blurred vision, ringing in ears, allergic reaction

Patients will be monitored in the post-operative care unit by nurses assigned to their care. Patients will have post-operative analgesics available for pain control that include 25mcg IV fentanyl for pain scores for breakthrough pain and Tramadol PO 25-50 mg for pain scores 4-10/10 as described above.

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

- **Cost to the Subject:**

Subjects will not incur any additional costs to participate in the study.

- **Data Analysis and Statistical Considerations:**

The primary hypothesis, that there is a difference in 24h opioid consumption between patients receiving an ultrasound guided regional block versus those receiving surgical field wound infiltration by the surgeon. We will also look at secondary outcomes evaluating numeric pain scores, GI complications (such as constipation and bloating and Nausea/Vomiting) and recovery between the two groups. Parametric and non-parametric data will be analyzed using t-tests, Chi-Squared, and Mann-Whitney tests as appropriate If there is evidence of a difference in numeric pain score during the periods studied, we will perform post-hoc pair-wise multiple comparison corrected tests to identify the time-points where the intervention groups differ on pain score. Additional secondary analyses will assess differences in cumulative opioid consumption in IV morphine equivalents, numerical pain scores, and functional assays with parametric or non-parametric tests as appropriate. Statisticians employed by the Department of Anesthesiology will conduct these analyses.

A total of up to 50 participants will be enrolled in the study in order to get 7-day follow up data from 40 participants. Participants will be randomized equally between Surgical Field Block and Regional Anesthesia groups based on sample size calculation for a non-parametric Mann-Whitney Test with a=0.05, b=0.8, difference in means=2, and effect size of 1.0. The sample size required for a non-parametric test will provide greater than 80% power if the data meet requirements for a parametric t-test (https://www.stat.ubc.ca/~rollin/stats/ssize/n2.html).

- **Data & Safety Monitoring:**

In accordance with federal regulations the PI will monitor for, review, and promptly report to the IRB and appropriate institutional officials, 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.

- **Privacy, Data Storage, & Confidentiality:**
    - Explain how you will ensure that the subject's privacy will be protected:
        - Potential subjects and their families will be approached 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
    - Describe how research data will be stored and secured to ensure confidentiality:
        - The research data will be collected and stored utilizing the RedCap database approved by Duke Health System. Only appropriate personnel involved in the study will be given access to the database.