INVESTIGATOR STUDY PLAN - REQUIRED

Comparison of Quadratus Lumborum Blocks with Medical Management for Pain Control after Lumbar Spine Fusion Surgery

NCT04588389

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1. Title

Comparison of Quadratus Lumborum Block with Medical Management for Pain Control after Lumbar Spine Fusion Surgery

2. External IRB Review History*

"NA."

3. Prior Approvals:
Departmental provisional approval. The Chair of Orthopedics has approved the project and we will only enroll subjects of the sub investigators listed on the project.

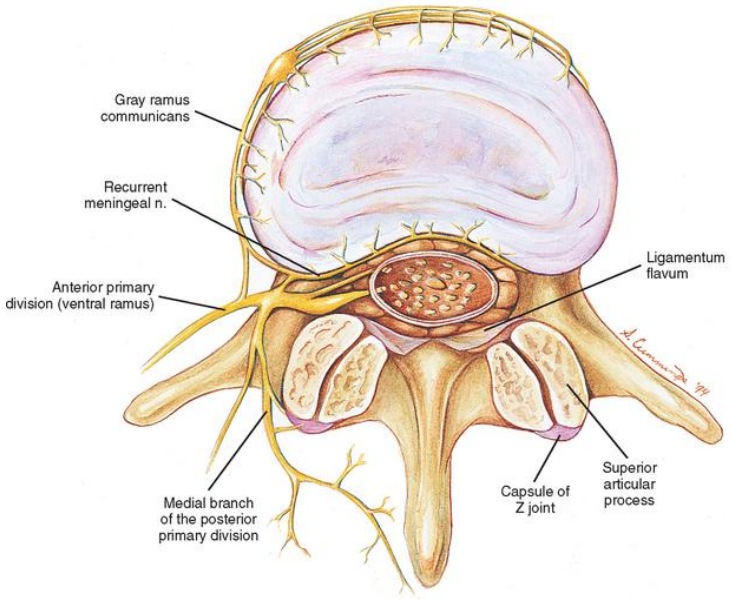
Conflict of Interest (COI):
No Conflict of Interest.

4. Objectives*
The objective of the study is to compare the opioid sparing effect and the quality of analgesia of quadratus lumborum plane block types 2 and 3 to systemic pharmacological management for postoperative pain control after lumbar spinal fusion.

Hypothesis:
Quadratus Lumborum plane block, when added to multimodal pharmacological management, will result in a reduced amount of opioids used postoperatively and better postoperative pain control than systemic pharmacological treatment alone.

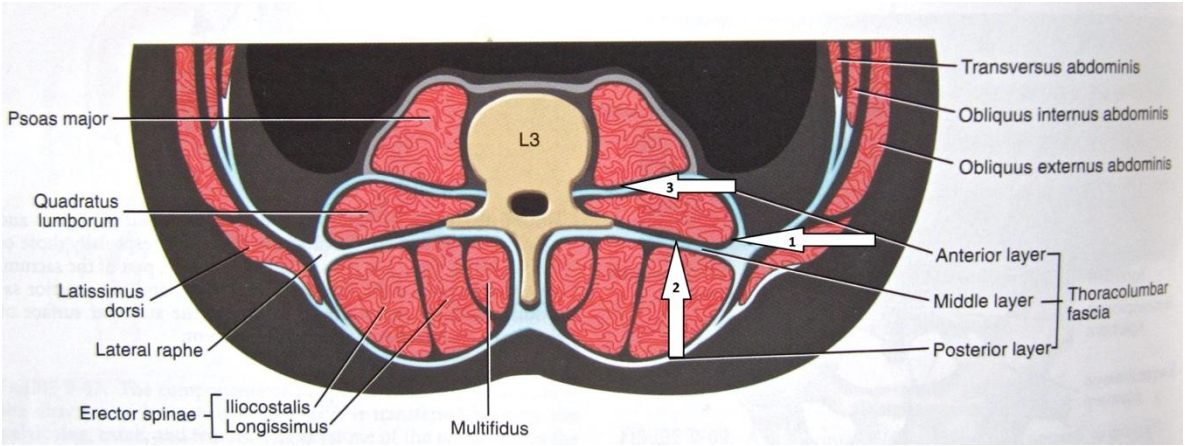
5. Background*
Patients undergoing spinal fusion surgery experience severe postoperative pain.[1] Inadequate pain control increases their morbidity and the development of complications. It also delays postoperative mobilization, rehabilitation and overall patient satisfaction with their perioperative experience.[2] The problem is compounded in opioid tolerant patients who need double or triple the amount of opioids needed to control the pain compared to the opioid naïve patients. [3, 4] The excessive use of opioids for postoperative pain management is one of the causes of the current opioid epidemic. Finding ways that can potentially reduce opioid consumption would be a valuable step in curbing this problem. Regional anesthesia using local anesthetics block the pain transmission from the injured site to the brain. It can provide excellent analgesia and help reduce systemic opioid consumption thereby reducing side effects. [5]

Lumbar spine innervation comes from thoracolumbar nerves originating from the spinal cord. The spine is divided anatomically into ventral, lateral and dorsal compartments in relation to intervertebral foramina. The ventral and the lateral compartments are supplied by the lumbar ventral rami of the spinal nerves and the lumbar plexus. The dorsal compartment is innervated by branches of the dorsal rami of the spinal nerves.[6]

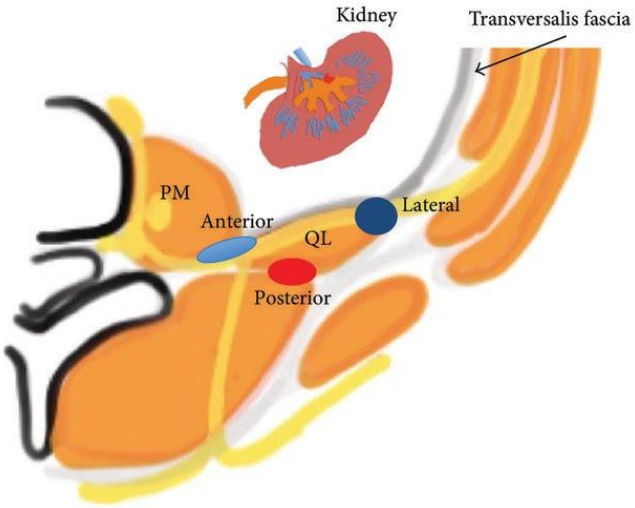


Treating postoperative pain from spinal fusion postoperative at UMMC is similar to other facilities that perform this procedure. The most commonly used treatment is multimodal medical management. The multimodal medical management uses opioid and non opioid medications, orally or intravenously. Opioids constitute the main componenet of treatment due to the severity of the pain and ceiling effect of the other non opioid medications. Finding a pain management method that can reduce the needed doses of opioids and improve the quality of pain relief is important. Case reports of using the quadratus lumborum block for pain relief after spinal surgery have shown promising results [10].

The Quadratum Lumborum Block (QL) is a fascial plane block that is successfully used for treating postoperative pain for abdominal wall surgery. Local anesthetics are deposited between the QL muscle and the plane formed by the thoracolumbar fascia (TLF). Currently, there are three types of the QL block. In the QL1 block, where the local anesthetic medications are deposited anteriorly on the lateral edge of the QL muscle. In QL 2 blocks they are deposited in the plane of the middle TLF posterior to the muscle. In the QL 3, they are deposited on the anteromedial aspect of the QL muscle and behind the psoas major muscle in the plane created by the anterior TLF.



The numbers on the arrows point to the type of block, 1 = QL1, 2= QL 2, 3= QL 3 Block



Red is QL 2, Blue is the QL3

It is thought that this nerve block works by local interruption of the impulse transmission as the nerves traverse the plane and also, by backtracking of the medication to the intervertebral foramina. Contrast studies of QL injections show that the contrast reaches the lower thoracic and upper lumbar nerve roots. For that reason, It is hypothesized that the QL block works as a paravertebral nerve block[7]. The QL 1 block does not seem to be beneficial in spine surgery as the local anesthetics spreads anteriorly towards the abdomen and therefore not be included in this study. [7, 8] It is plausible that performing either a QL 2 or QL 3 block would result in good pain relief by blocking the nerve roots and by the direct relaxation of the muscles that are supplied by those nerves. The other values of the QL-block are the simplicity, and the absence of major blood vessels in the area as well as the ability to perform it without interference with the surgical site.

6. Inclusion Criteria:

- Adult Patients undergoing lumbar spinal fusion surgery.
- Patients from 40-70 years.

Exclusion Criteria:

- Recent drug abuse
- History of illicit drug use
- Chronic pain patients not related to the back lesions.
- Opioid tolerant patients.
- Patients with any lower extremity weaknesses or deficits.
- Patients with ASA classification more than 3.
- Coagulopathy.
- Infection near or in the area of the block.
- Pregnant patients.

- Uncooperative patients who refuse care which directly effects research participation or clinical care.
- If the surgeon reports performing non-typical fusion,
- The presence of intraoperative complications like nerve injury or abnormal results of neuromonitoring and extensive dissection.
- Vulnerable populations (prisoner, mental impairment / dementia, pregnant, etc.)
- Subjects on chronic buprenorphine therapy (either for opioid replacement or pain control)

7. Study-Wide Number of Subjects*

This study is a pilot study as part of planning for a larger randomized controlled trial. We plan to enroll a total of 30 patients, with 10 patients randomly assigned in each group of the study. Group I will receive multimodal pharmacological management (control group). Group II will receive the QL II Block and group III will receive the QL III block in combination with multimodal pharmacological Management. [9, 10]

8. Study-Wide Recruitment Methods*

After coordination with the orthopedic surgeons from the spine division, patients scheduled for an elective lumbar spinal fusion will be identified and screened on the electronic charts by the investigators. Patients who meet the inclusion criteria will be approached and provided with all the study information in the presurgical evaluation (PSE), the spine surgery clinics, or the hospital floor. Patients who agree will be asked to sign the informed consent. For those who need more time to think or could not be reached physically but expressed interest to the surgeon, a study team member will be contacted them by phone and provide all the information and the patient will sign the informed consent on the day of surgery. The study will start as soon as the IRB approves the protocol. The location of the study will be at the UMass Memorial Medical Center, Memorial campus.

9. Study Timelines*

Patients are expected to participate in the study for the first 48 hours after surgery and the first postoperative visit about 2 weeks from the time of surgery. The primary analyses are expected to be completed 6 months after conclusion of the study. This is intended to be a pilot study; we estimate it to be completed 18 months from the IRB approval date.

10. Study Endpoints*

Primary Outcome:

- Fifteen percent drop in MME dose of the opioids consumed at 12, 24, 36 and 48 hours.

Secondary Outcome:

- The NRS every six hours 0, 1, 6, 12, 18, 24, 30, 36, 42 and 48 recorded by nurses in the EPIC flow sheet will be used to collect the data at the approximate time intervals.
- The amount of left-over opioid pills at 2 weeks in the follow up visit.
- The presence of any side effects will be reported.

  - Nausea and vomiting
  - Sedation.
  - Motor weakness.
  - Excessive numbness or paraesthesia.
- Other side effects.

11. PROCEDURES INVOLVED*

- After coordinating with the orthopedic surgeons from the spine division, potential candidates will be contacted (in the clinics or the floor as above) and the study will be thoroughly explained to them by the research staff, PI or sub investigators.
- Informed consent will be obtained from the patients who are willing to participate.
- All study patients will be randomized to receive either multimodal pharmacological management only or with one of the 2 blocks- QL 2 block or QL 3 - using a sealed envelope.
- The study patients will be revaluated before surgery and their consent will be confirmed.
- Anesthesia is a standard general anesthesia where opioids will be used based on the discretion of the anesthesia provider.
- After their surgery is completed and the leg movement is tested, the patients will receive the block in the operating room or in the post anesthesia care unit (PACU), their pain will be evaluated and documented by the nurse caring for the patient.
- For the blinding purposes, the patients will be told that there are two possible sites at which they will receive the block. The sites will be either in the operating room before you wake up from anesthesia or in the PACU. The patients on the medical management group will be told that they have received their block before recovering from anesthesia, the PACU nurse will be told the same as well to make him or her blinded as a pain assessor.
- For those who will have the block, the procedure will be as follows: the hip will be raised on the side of the block and the area between the iliac crest and costal margin is scrubbed using chlorhexidine solution. Under complete aseptic technique including a sterile ultrasound probe sleeve and ultrasound guidance, 20 ml of ropivacaine 0.25 % will be injected in the facial planes as decided by the randomization envelope. The procedure will be repeated on the other side.
- The patient's vital signs will be recorded every 5 minutes for 30 minutes after the procedure.
- The pain score will be recorded, and the patient will be examined for signs of sensory and motor blockade after 1 h using the following score:
  Muscle strength using the Medical Research Council (MRC Scale)[11]
  0= Complete Paralysis
  1=Minimal Contraction.
  2=Active movement with gravity eliminated.
  3=Weak contractions against gravity.
  4= Active movement against gravity
  5= Normal strength.

The dermatomes will be tested for sensory blockade using ice. See Figure 1.

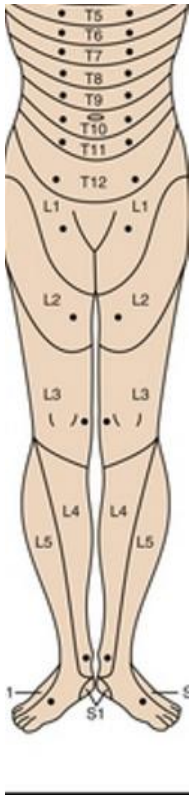


Figure 1: Dermatomes of interest

Table I: Motor Blockade

	R	L	Group of Muscles	MRC Muscle Strength					
				0	1	2	3	4	5
L2			Hip Flexors						
L3			Knee Flexors						
L4			Ankle Dorsiflexes						
L5			Long toe Extensors						
S1			Ankle plantar flexors						

All the patients will receive a multimodal pharmacological management comprised of the following medications:

- Oral acetaminophen, intravenous Ketorolac (Toradol) and Gabapentin.
- Opioids:
    - Oxycodone q 4 hours as needed based on the patient's pain

Patients with pain 3-4 on NRS will receive 5 mg; pain from 5-7, they will receive 10 mg; pain from 8-10 they will receive 15 mg.

- As needed PRN intravenous hydromorphone 0.2 mg q 2hs.

12. Data and Specimen Banking*:
"NA"

13. Data Analysis and Management*:
The primary analysis of interest is the comparison of the reduction in morphine milligram equivalent (MME) dose of opioids consumed between the multimodal pharmacological management (control group) versus nerve block (QL II and QL III) groups. Specifically, we hypothesize that people receiving a nerve block will have less opioid consumption per day for 48 hours than people receiving standard-of-care. To answer this question, we will use a two-sample t-test of means with unequal n's comparing MME between the two groups (control vs nerve block (QLII & QLIII)). Although not directly powered to do so we will also determine if a difference exists in MME doses between the two nerve block groups (QLII & QLIII) using a similar approach as described above.

As a secondary outcome we will also utilize the Numeric Rating Scale for pain scores to be measured every six hours for 48 hours (8 measurements). We will compare pain scores between control vs. nerve block groups using a repeated measures ANOVA model. We will also repeat these analyses looking for a difference between all three groups.

Allocation of participants to study arms will be based on a permuted block scheme in which treatment assignments are made within blocks so that numbers assigned to each treatment arm are equal after a block has been filled. Blocks of various sizes will be used in random order to facilitate allocation concealment. The randomization process will be facilitated using a prime modulus multiplicative pseudo-random generator.

Secondary Outcome:

- The VRS every six hours 0, 1, 6, 12, 18, 24, 30, 36, 42 and 48 recorded by nurses in the EPIC flow sheet will be used to collect the data at the approximate time intervals.
- The amount of left-over opioid pills at 2 weeks follow up visit.
- The presence of side effects will be reported.
    - Nausea and vomiting
    - Sedation: using Pasero Opioid-induced Sedation Scale (POSS)
        - 1 = Awake and alert
        - 2 = slightly drowsy, easily aroused Acceptable.
        - 3 = frequently drowsy, arousable, drifts off to sleep during the conversation.
        - 4 = Somnolent, minimal or no response to verbal and physical stimulation
    - Motor weakness.
    - Excessive numbness or paraesthesia
- Other side effects.

14. Provisions to Monitor the Data to Ensure the Safety of Subjects*
The principal investigator will be responsible to review the data periodically to assess the outcome of the study. Severe complications related to the block like deep-seated infection, hematoma formation that needs surgical intervention or irreversible leg weakness or nerve damage will be reported immediately and may trigger suspension of research.

15. Withdrawal of Subjects Without Their Consent*
"NA"

16. Risks to Subjects*
Patients might feel some discomfort on the introduction of the needle to place the block; however, local anesthetic infiltration of the skin will be used to minimize this discomfort. Other side effects are rare but can be in the form of a mild temporary leg weakness. The motor strength of the lower extremities will be checked within the first one hour after the block. If leg weakness does not happen in the first hour then it will not happen. During this period the patient will be in the recovery room and under continuous monitoring

While rarely reported, if leg weakness should happen it will be mild and temporary due to the low concentration of the local anesthetic, and the type of the local anesthetic we use. Ropivacaine has preferential sensory blockade rather than motor blockade. We also will be using the dilute form which is 0.25% of Ropivacaine and is known to have minimal motor blocking properties if at all[12, 13]. As stated above, the motor strength of the lower extremities will be checked one hour after the block, which will be sufficient time to show this potential side effect. If it occurs it will present within the first hour after the block while the patient is in the recovery room and under continuous monitoring. Patients and the floor nurse will be made aware that that patient should not move out of bed in absence of personal assistance. One of the investigators will follow up with the patient until the weakness resolves. Other possible extremely rare risks include infection, hematoma and persistent neuropathy. The patients will be examined every day during their hospital stay. After discharge the patients will be able to contact the primary spine surgery service that will notify the PI. All the necessary intervention will be done as the case dictates.

17. Potential <u>Direct</u> Benefits to Subjects*
The potential benefits to the patients are:

- Better pain relief following a significantly painful surgery.
- Reduced opioid use.
- Earlier participation in rehabilitation, faster recovery and hospital discharge.

18. Vulnerable Populations*
The study does not intend to include any vulnerable patients.

19. Multi-Site Research*
"NA"

20. Community-Based Participatory Research*
"NA"

21. Sharing of Research Results with Subjects*
Upon conclusion of the study, patients can contact the study PI for the results of the study.

22. Setting:
The study will take place locally at the UMASS Memorial Medical Center, Memorial campus. Explanation of the study will take place in the PSE, spine clinic, the hospital floors, by the phone and /or the in the preoperative holding area. Nerve block procedures will be performed in the post anesthesia care unit (PACU) after surgery is completed. The follow up will happen on the hospital floor.
The data will be accessed and stored safely on a secured server.

23. Resources Available:
Specific anesthesiologists specialized in regional anesthesia will administer the nerve blocks for all subjects involved in this study.

Roles
PI: The PI will plan the study, oversee the whole process, perform some of the blocks, receive the results, interpret the results after the statistical analysis is done and write the manuscript. The PI is an anesthesiologist who is trained in the subspecialty of regional anesthesia.

Sub investigators: Assist in the study planning, performing the blocks, following the study and writing the manuscript. The co-investigators are anesthesiologists who are trained in the subspecialty of regional anesthesia and orthopedic surgeons who operate on the patients.

Research coordinators/Nurse: Will assist in formulating the study plan, randomizing, explaining the study to potential participants, and collection of data. The research coordinators are nurses or research coordinators who are experienced in conducting research.

24. Local Recruitment Methods
As a pilot study, we will plan to do 10 cases in each group. Patients will be screened for eligibility based on the inclusion criteria and exclusion criteria, adult patients undergoing 2 or more levels of lumbar fusion, with no chronic pain issues other than back pain. The patient's medical record number will be the identifier used to screen the patient records. Patients who agree to participate will be evaluated and consented. Patients who turn out to be ineligible to

participate after the initial consent will be informed of the reason. After the patient who enter the study, will be given a study code and their data will be saved under that code and no identifier will be linked to the data.

25. LOCAL NUMBER OF SUBJECTS: We plan to enroll 30 subjects.

26. CONFIDENTIALITY

Data of each study patient will be collected by study members and entered in a spreadsheet. Each coauthor will hand the data of the cases they do to the PI and the research coordinators. Only the PI and the research coordinators will have access to all the data. The data will be stored in a secure server location assigned to the study. Each patient data will be entered under a code assigned to them.

The data that will be stored is the study patients are the following:

- Age
- Gender.
- Details of the surgical procedure: anterior/ lateral level and number of fusion, number of levels fused.
- Type, dose of opioids used preoperatively and their MME doses.
- Type, dose of opioids used intraoperatively and their MME doses.
- Type and total MME doses every 12, 24, 36 and 48.
- Types and doses of non-opioids analgesics and adjuvants (e.g. Acetaminophen, non-steroidal anti-inflammatory drugs, gabapentin, clonidine.
- Side Effects:
  - Muscle weakness.
  - Excessive numbness.
  - Other side effects.

Storage: The source data will be stored in the critical care research office. The Critical Care Research office is secured with a keypad lock. The combination is known only to authorized individuals. The electronic data will be kept on UMASS secure servers and protected in a database that is password protected and encrypted. Data will be stored in the password protected secure files.
Each study patient data will be de-identified and given an ID number and all their data will be saved under that ID.

Data: All data will be transmitted to the PI and the research coordinators who will store the data on a secure server. Data will be tabulated in excel tables. Descriptive statistics will be used describe data. Comparison of data will be done using two-way ANOVA

27. Provisions to Protect the Privacy Interests of Subjects

A HIPAA waiver of authorization will be used to screen any subjects after the surgeons send the patient names as appropriate candidates for this research study. The subjects will be made comfortable and given enough privacy during and after all the steps of the research. Drapes and curtains will be used during the procedure, local anesthetic medication will be used to infiltrate the target pathway. Patient will be informed that they have the right to skip any question they don't wish to answer.

Only research personnel involved in the research study and trained to conduct the study related procedures will be involved with the subjects.

28. Compensation for Research-Related Injury

Neither subjects nor their insurance will be billed for research procedures. The University of Massachusetts Medical School does not provide funds for the treatment of research-related injury. However, if the subject is injured as a result of their participation in this study, treatment will be provided. The subject or their insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available.

29. Economic Burden to Subjects

Subjects will not incur any cost from being in the study. All study related charges will be paid internally through the department, as per the charges generated by Investigational Drug Services (IDS).

30. Consent Process:

Where will the consent process take place: The consent process will take place in the presurgical evaluation (PSE), the spine surgery clinics, or the hospital floor.

Any waiting period available between informing the prospective subject and obtaining consent: The subject will be given as much time as possible to decide whether they would like to participate in the research study. All questions will be discussed. If the subject is not comfortable making a decision, the subject will not be enrolled.

Informed Consent Process: The principal investigator will ensure that informed consent is obtained in accordance with the SOP: HRP-802 INVESTIGATOR GUIDANCE: Informed Consent". Those obtaining informed consent from the subject will be a PI, sub investigator, research nurse, research nurse manager or research coordinator who has been properly trained by the principal investigator, is knowledgeable about the study and able to answer any questions the potential subject may ask.

After discussing the study in detail (risks, procedures, follow-up) the subject will be given the informed consent form to review. The subject will be asked if they understand what has been explained. All questions will be discussed. If they are uncomfortable or hesitant about participating in the research, the consent process will be stopped. If the subject is willing to participate in the research, they will sign and date the informed consent form. The research staff personnel obtaining consent will sign and date the forms where appropriate. A copy of the ICF form will be given to the subject. The original ICF will be placed in the regulatory binder for the research study. A copy of the ICF form will be placed in the subject's medical record.

A note will be placed in the subject's electronic medical record noting the following:

- The date and time that the informed consent form was signed
- Discussion of the study and questions answered
- That the subject met all study entry criteria

31. The process to Document Consent in Writing

We will be following the "HRP-803 INVESTIGATOR GUIDANCE: Documentation of Consent."

32. Drugs or Devices:

The drug that is going to be used in the study is Ropivacaine 0.25% diluted in saline to 0.2 %. The ultrasound machine will be used to guide the block. The study medication will be administered by a licensed professional who is appropriately knowledgeable in the administration of the study drug. All study drugs have been coordinated with Investigational Drug Services.

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