PROTOCOL

Rectus Sheath Block and Coadministration of Intravenous Dexamethasone for Analgesia after Pediatric Laparoscopic Appendectomy – A Pilot Study

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1. INTRODUCTION

One in three pediatric patients who undergo a laparoscopic appendectomy experience substantial post-operative pain.[1] Post-operative pain often results in the prescription of opioid medication that can delay recovery due to its side effects of sedation, respiratory depression, nausea, and constipation; all of which can lead to postoperative complications, patient dissatisfaction, and delayed discharge.[2] In the pediatric population, laparoscopic appendectomies result in approximately two-thirds of patients requiring post-operative opioids despite the routine use of local anesthetic (LA) infiltration at the incision sites by the surgeon.[3] There is a need to optimize the analgesia management of these patients. Regional anesthetic techniques for analgesia in pediatric abdominal surgeries reduce opioid requirements, enhance recovery time, and have a proven safety record.[4,5,6] Specifically, the rectus sheath block (RSB) is a regional technique for pediatric laparoscopic appendectomies.[7,8] An RSB specifically delivers LA between the rectus muscle and the posterior sheath on either side of the umbilicus to anesthetize the intercostal nerves. The randomized control trial (RCT) by Hamill et al. demonstrated that RSBs reduced global pain scores in uncomplicated pediatric laparoscopic appendectomies as compared to saline infiltration in the anesthetic care unit (ACU), but did not significantly reduce 24-hour opioid consumption or reduce the length of ACU stay.[7] Similarly, a retrospective study by Maloney et al. demonstrated both reduced pain scores and opioid consumption in the ACU when an RSB was administered. Despite these promising results, the analgesic benefits of an RSB appear to diminish within the first 6 to 8 hours.[6] This is not unlike other single-shot peripheral nerve blocks, where the duration of analgesic effects is traditionally between 8 and 14 hours.[9] The use of LA adjuncts, such as dexamethasone, has been shown to extend the duration of LA.[10] Intravenous (IV) dexamethasone is recommended due to its ability to prolong peripheral nerve blocks and its limited side effect profile.[9] A Cochrane review determined that IV dexamethasone increased block duration by 6.2 hours and reduced cumulative 24-hour opioid consumption in comparison to a placebo.[11]

Data from a 2021 audit at our institution suggests approximately 25% of laparoscopic appendectomy patients had a postoperative pain score of 7 or higher in the ACU and required

opioids to control their pain. Furthermore, it is standard to admit all patients who undergo laparoscopic appendectomies postoperatively at our institution. This contrasts with pediatric hospitals across North America that have transitioned to same-day discharge (SDD) for uncomplicated cases. SDD has proven to be a safe, feasible, and cost-effective approach.[12,13,14,15] Many SDD pathways utilize regional anesthetic blocks, such as RSB, to help facilitate discharge[16].

2. STUDY RATIONALE

The goal of this study is to improve post-operative pain control for pediatric laparoscopic appendectomy patients by comparing two methods of anesthetic delivery.

(1) RSB+dex: an RSB with a coadministration of IV dexamethasone as an LA adjunct, administered by the anesthesiologist.

(2) LA: LA infiltration alone, administered by the surgeon.

While both (1) RSB+dex and (2) LA are standards of care at BC Children's Hospital, it is currently unclear which is a superior post-operative analgesic option. Furthermore, to our knowledge, no study has evaluated the addition of an LA adjunct to an RSB to prolong the analgesia effect in this population. We hypothesize that performing (1) RSB+dex will provide superior pain control postoperatively compared to (2) LA. To evaluate this hypothesis, we will conduct a pilot study by allocating pediatric laparoscopic appendectomy patients to either (1) RSB+dex or (2) LA. Postoperative opioid requirements, postoperative pain scores, and parent satisfaction with recovery will be assessed. By conducting a pilot study, we plan to estimate the efficacy of an RSB+dex to ensure the study design is optimized prior to engaging with a large, multicenter RCT. If an RSB+dex provides superior postoperative analgesia, these results may help guide management at our institution for implementing an SDD pathway for pediatric laparoscopic appendectomies. The RSB is a basic regional technique due to its simplicity and reliability.[17] The low cost, minimal risk, and the short amount of time necessary to perform it make the RSB an ideal regional anesthetic for widespread implementation.

3. AIM OF STUDY

To compare postoperative analgesia between (1) RSB+dex group: an RSB with a coadministration of IV dexamethasone as an LA adjunct and (2) LA group: LA infiltration alone by the surgeon in pediatric patients undergoing a laparoscopic appendectomy for uncomplicated appendicitis.

4. HYPOTHESIS

Patients receiving in the (1) RSB+dex group, will have superior analgesia compared to patients in the (2) LA group, as evidenced by reduced postoperative opioid consumption and pain scores.

5. OUTCOMES

a. PRIMARY

i. To determine the total opioid administration from the start of surgery until discharge in each group.

b. SECONDARY

i. To determine time spent performing the RSB block.

ii. To determine the time in the ACU for each group.

iii. To assess the duration of post-procedural hospitalization for each group.

iv. To assess the parental perspective of patient recovery.

Total opioid administration will be calculated by converting all administered opioids, excluding remifentanil, to morphine per kilogram equivalents. The duration of time performing RSBs will be recorded by the anesthesia team in the online record within the RSB procedural note. Time performing the block will commence post-induction of anesthesia when the anesthesia team has secured the airway, and the maintenance stage of anesthesia is initiated. The performance of the RSB block will be considered complete at the end of the local anesthetic injection. The first post-procedural pain score recorded in ACU will be considered time 0 hours. The subsequent pain scores recorded closest to the study time points (i.e., 4 hours, 8 hours, 12 hours, and 16 hours post-operative) will be used for mean post-operative pain scores. Time in

ACU is recorded in the online patient record via post-operative arrival and departure times recorded by nursing staff. Average pain scores and non-prescription drug requirements will be collected via a post-operative parent survey. No changes to the study outcomes will be made after study commencement. See Table 1 below for further details.

Table 1. Study Endpoints

Clinical Objectives	Outcome	Outcome Measure	Variables	Hypothesis	Analysis
Primary					
1. Difference in total opioid administration from start of the surgery until discharge	Mg/kg morphine equivalents	Continuous: Measured by collecting and totaling all opioid (excluding remifentanil) administrations from intraoperative, ACU, and ward records and converting to morphine milligram per kilogram equivalents.	Treatment group	RSB+dex < LA	Mean difference (95% CI)
Secondary					
2. To determine the mean postoperative pain score at 12 hours for each group	Visual analog pain scores	Discrete: Pain: Measured via age-appropriate visual analog scales (FACES Pain Scale-Revised for age < 12, Numeric Rating Scale for age > 12)	Treatment group	RSB+dex < LA	Mean difference (95% CI)
3. To assess if pain scores at 0 hours, 4 hours, 8 hours, and 16 hours postoperative differ between groups	Visual analog pain scores	Discrete: Pain: Measured via age-appropriate visual analog scales (FACES Pain Scale-Revised for age < 12, Numeric Rating Scale for age > 12)	Treatment group	RSB+dex < LA	Mean difference (95% CI)
4. Determine the time spent performing RSB	Time (mins) recorded by anesthesiologist	Continuous Time: measured in minutes	N/A	N/A	Mean time (mins)

5. Determine the duration of ACU stay	Time-to-ACU discharge	Continuous Time: measured in minutes	Treatment group	RSB+dex < LA	Mean difference (95% CI)
6. Determine the duration of post-procedural hospitalization	Time-to-hospital discharge	Time-to-event: Event: discharge from hospital Time: Duration of time from entering OR to hospital discharge in minutes.	Treatment group	RSB+dex < LA	Hazard Ratio (95% CI)
7. Determine the parental perspective on patient post-operative pain	Numeric analog pain scores	Discrete: Pain: Numeric rating scale	Treatment group	RSB+dex < LA	Mean difference (95% CI)
8. Determine which non-prescription drugs were administered post-operatively	Mg/kg	Continuous: Measured by collecting and totaling all non-prescription drugs provided by the parent to the child post-operatively	Treatment group	RSB+dex < LA	Mean difference (95% CI)
9. Parental satisfaction with recovery	Likert scale	Discrete 5-point scale Very unsatisfied Unsatisfied Neutral Satisfied Very satisfied	Treatment group	RSB+dex > LA	Mean difference (95% CI)

6. METHODS

a. Study Design

This will be a single-center pilot study conducted at British Columbia Children's Hospital (BCCH). The methods will not be modified during the study.

b. Participant Eligibility

i. Inclusion Criteria

- Age 4-18 years old*
- Diagnosed with acute appendicitis.
- Undergoing a laparoscopic appendectomy

ii. Exclusion Criteria

- Perforated/complicated appendicitis diagnosis
- Previous abdominal surgery
- Allergy to bupivacaine or dexamethasone
- Severe developmental delay preventing patients from using pain scales or adequately communicating pain**
- Patients with Type 1 or 2 diabetes mellitus***
- Patients with steroid dependence

*The pain scale (FACES revised) used for this study has been validated in children as young as 4 years old. This age range will ensure all eligible patients who can be evaluated using this tool are captured in our research. Medications used in this study (bupivacaine and dexamethasone) are approved for this age range.

**The Face. Legs, Activity, Cry, and Consolability (FLACC) Scale may be used to determine pain in patients with severe developmental delays. However, we cannot effectively compare FLACC scores with the FACE scores used in our study.

***In some instances, a dose of dexamethasone can increase blood glucose levels for up to 24 hours post-administration. Some families and surgeons may be hesitant to administer this medication to diabetics, as increased blood glucose levels could increase their likelihood of perioperative adverse outcomes.

Patients will be assessed for study eligibility by research personnel or by care providers for after hours cases. If eligibility criteria are met, patients will be randomized into one of two groups (RSB+dex or LA). Per current standard of practice at BCCH, the anesthesiologist will explain the surgical plan/intervention and any associated risks to the patient during the anesthesia consultation, prior to surgery.

c. Sample Size

This pilot study is designed primarily to estimate the efficacy of our approach to RSB and help guide a future, larger RCT. There are approximately 70-80 cases of uncomplicated laparoscopic appendectomies per year. We estimate it will take 7-8 months to reach 32 patients for the study if 70% of cases are eligible and consent to participate. Therefore, a convenience sample of 16 participants per group (32 patients total) is pragmatic given our local case numbers at BCCH. With a significance level of 0.05 and assuming an outcome standard deviation of 0.01 mg/kg,[8] we will have 100% power to detect a minimum difference of 0.02 mg/kg opioid administration between groups. With a significance level of 0.05 and assuming an outcome standard deviation of 0.15,[8] we will have approximately 95% power to detect a minimum difference of 0.2 in mean postoperative pain scores between groups.

d. Randomization

Patients will be randomized to 1 of 2 groups. The randomization sequence will be computer-generated using varying blocks of 2 and 4 randomization. The randomization sequence will be concealed from the postoperative care team. Sealed envelopes will be created according to the sequence and placed in the BCCH Department of Anesthesia's Research Office for either the anesthesia team or research personnel to obtain and open when a new participant is deemed eligible. All randomization and group allocation documents will be kept in the BCCH Department of Anesthesia's Research Office.

e. Recruitment and Blinding

All laparoscopic appendectomy cases who are already in the hospital and booked at BCCH will be considered as potentially eligible. We will submit a request for deferred consent under

TCPS2 Article 3.7A with our ethics application. No patients (or parents) will be recruited prior to surgery. The patient and their parent(s) will be informed by the anesthesiologist that due to their surgery type; they will be approached by research staff after surgery. We request the need for deferred consent from the Research Ethics Board (REB), justified according to TCPS2 Article 3.7A as it fulfils the following points.

a. *The research involves no more than minimal risk to the participants.*

Both possible interventions are standard of care and are regularly used at BCCH. Participation in this study will not pose any additional risk than receiving a laparoscopic appendectomy at BCCH already would. Additionally, the patient will not be blinded to their group allocation. Anesthesiologists will provide their standard preoperative consult to the patient, where they will explain any risks associated with being under anesthesia and where the patient will have the opportunity to ask questions. As is standard practice at BCCH, patients will provide surgical and anesthetic consent.

b. *The alteration to consent requirements is unlikely to adversely affect the welfare of participants.*

The alteration to consent will allow patients and their families consent outside the hospital, where they will not face the stress of additional decision in an overwhelming, painful (for the patient), and emergent situation. The alteration to consent will allow a more clear and thoughtful consideration of consent and participation. Additionally, the alterations are unlikely to adversely affect the welfare of study participants because both interventions are standard of care. The treatment participants receive as being part of the study will be no different than the treatment they may have received without participating in the study. Following the surgery, participants will have the opportunity to decline to consent in the research study.

c. *It is impossible or impracticable to carry out the research and to address the research question properly, given the research design, if the prior consent of participants is required.*

Due to the emergent nature of laparoscopic appendectomies, it is impracticable to recruit a representative participant pool without an alteration to consent. Cases done after hours may be more severe or painful than cases done during working hours. Deferred consent will avoid bias being introduced into the study. Additionally, it is not feasible to have the anesthetic care team or health care providers recruit participants.

d. *In the case of a proposed alteration, the precise nature and extent of any proposed alteration is defined.*

All laparoscopic appendectomy patients who meet study eligibility criteria at BCCH will be randomized to one of two interventions that are standard of care (RSB+dex or LA). The anesthesiologist and the participant will not be blinded to their group allocation, allowing the anesthesiologist to present the risks associated with the anesthetic intervention to the patient. The anesthesiologist will inform the patient that due to their surgery type, a research staff member may follow-up with them after their surgery to invite them to participate in a study, at which time they could provide or decline consent. Following the surgery (24 to 48 hours post-op) a research staff member will call the patient's parent or guardian to recruit them for the study. The parent will then choose to provide informed consent, and the child will choose to assent to participate if age appropriate. If the patient chooses to participate, we will collect data from their chart and forward a post-discharge parent follow-up survey via REDCap. We will call the patients' parent or guardian up to three times to recruit the patient for the study. If we cannot reach the parent or guardian, or if they decline to provide consent, the patient will not be enrolled in the study.

e. The plan to provide a debriefing (if any) that may also offer participants the possibility of refusing consent and/or withdrawing data and/or human biological materials, shall be in accordance with Article 3.7B.

The patient and their parent will be recruited by phone 24 to 48 hours post-operatively. At this point, participants will be given the opportunity to either consent or decline to participate. During this phone call, the study will be explained to the patient's parent and their questions will be answered. If they choose to participate, they will be emailed a REDCap e-consent form and a link to the parent follow-up survey. If they decline to participate, no data will be gathered from their chart.

Participants will not be blinded to the anesthetic technique the receive, but they will not be aware that they were randomized. Therefore, we do not anticipate that the patient's group allocation will bias their post-operative pain scores or post-operative opioid requirements. As per our standard practice, ACU nurses will be informed of the total local anesthetic dose administered to each participant. Nurses collecting pain scores and assessors completing the data collection will be blinded to the patient's group assignment. We are unable to blind research personnel who will be retrospectively collecting data from the BCCH medical record system and entering directly into REDCap. However, data analysts will be blinded to group allocation until analysis scripts are finalized.

The intraoperative team will not be blinded to the anesthetic technique used, thus unblinding in case of emergency in the operating room is unnecessary. In terms of recovery, both patient groups will receive the same single dose administration of the medication (local anesthetic bupivacaine) but delivered in different methods. Should an emergency arise, the blinded recovery nurse's management will be the same for either group. The different techniques should not differ in terms of local anesthetic absorption or uptake, as the injection sites are in a similar area of vascularity.

f. Study Arms and Anesthetic Protocol

There are 2 groups: (1) RSB+dex versus (2) LA. Both interventions are current standards of care for appendectomy patients and are used by providers at BC Children's Hospital. Each group will receive up to a maximum of 1 mL/kg total of LA which will ensure the total volume calculation for each arm would receive a bupivacaine dose at or below 2.5 mg/kg body weight. The anesthesia team will perform the bilateral RSBs using an in-plane ultrasound-guided technique with 0.25% bupivacaine with epinephrine 1:200 000 at 0.8 mL/kg (half of total volume per side) up to a maximum of 20 mL. The surgical team will then use the remaining 0.2 mL/kg to infiltrate the remaining port sites in the RSB+dex group. The LA group will receive the same LA (0.25% bupivacaine with epinephrine 1:200 000). Surgeons can inject up to a total dose of 0.8 mL/kg (maximum 20 mL) at the umbilical port site. The remaining volume of LA (0.2 mL/kg) can be infiltrated at each of the incision sites at the discretion of the surgeon. Both study medications (bupivacaine and dexamethasone) being used in this study are approved for the age range in this study.

Anesthesiologists can provide intraoperative analgesia such as fentanyl (max 5 mcg/kg), morphine (max 0.15 mg/kg), hydromorphone (max 0.02 mg/kg), ketorolac (max 0.5 mg/kg), acetaminophen (max 15 mg/kg), dexmedetomidine (max 0.5 mcg/kg) at their clinical discretion, to ensure quality of care is maintained and that the varying needs of patients are met. Preoperative acetaminophen or ibuprofen given within 4 hours of surgical incision will be included in the analysis. No other significant source of LA administration (e.g., lidocaine infusion) or ketamine will be permitted. Postoperatively, each participant will receive scheduled acetaminophen (20 mg/kg PO q6hr, max 1 g) and ibuprofen (10 mg/kg PO q6hr, max 400 mg) for 24 hours. Other postoperative analgesic drugs can be administered by ACU and ward nursing staff as prescribed. Monitoring and safety measures for each group will follow standard BCCH protocols. The anesthetic protocol is all within the standard scope of anesthesia care that is normally provided for this patient population, as both these techniques are standard practices of care at BC Children's Hospital. We will be following the standards of care for intraoperative and postoperative monitoring that are already in place at BC Children's Hospital. The potential risks of this study are the same risks that apply to every appendectomy case at BC Children's Hospital.

g. Data Collection

All data, except the parent survey, will be gathered retrospectively from electronic medical charts by research assistants and input into REDCap electronic data capture tools.[18,19] See the data collection form for the participant characteristics that will be collected to assess group similarity. The parent survey will be conducted via REDCap after the patient is recruited to the study.

h. Implementation

The primary investigator for this project is Dr. Prakash Krishnan. Dr. Hannah Piper will be the lead surgical investigator. All investigators are responsible for initial study conception, protocol design, and randomization generation. Consultations with pediatric general surgeons and nursing colleagues in the ACU and surgical ward assisted in study design. Before the study launch, anesthesia department providers will be briefed on the study protocol, recruitment, data collection, and example conduct of RSB blocks (see Appendix Figure 2).

i. Statistical Method

Please refer to the outcomes section, table 1 study endpoints, for anticipated data analysis. The primary investigators and the department statisticians will perform statistical analysis. Descriptive statistics will be used to describe participants' characteristics. Counts and percentages will be presented for categorical variables; means and standard deviations for normally distributed continuous variables; and medians and quartiles (Q1 and Q3) for non-normal continuous variables. Mean differences and corresponding 95% confidence intervals (CI) will be reported to capture the differences in treatment group for outcomes (i) mean total opioid administration from the start of surgery until 24 hours postoperatively, (ii) pain scores at 0 hours, 4 hours, 8 hours, 12 hours, and 16 hours post-surgery (iii) duration of time performing RSB, (v) duration of time in ACU, and (vii) parental satisfaction using linear regression models. Hazard ratios and corresponding 95% CI will be reported to capture the differences in the treatment group for time-to-hospital discharge using Cox proportional hazards models. The Likert scale scores from the parental survey will be analyzed via a Mann-Whitney test and ordinal logistic regression model.

j. Knowledge Translation

Results will be presented at BCCH Department rounds, E2i and UBC Department of Anesthesiology, Pharmacology, and Therapeutics Research Days, and at targeted conferences, including the International Anesthesia Research Society and the Canadian Pediatric Anesthesiology Society's annual meetings. We will prepare a manuscript(s) for appropriate peer-reviewed journals. Targeted publications include Pediatric Anesthesia, the Canadian Journal of Anesthesia, and the Journal of Pediatric Surgery.

There is an opportunity for the study results to help shape clinical practice at BCCH. The most efficacious pathway for postoperative analgesia for laparoscopic appendectomy has yet to be determined and variance among our anesthesiologists exists. If one method appears superior, this may assist in developing a pathway/guideline for care. Furthermore, the results may suggest that a larger RCT is required to accurately conclude if one approach is superior, and if so, this could broaden the effect on clinical practice outside of BCCH.

7. APPENDIX

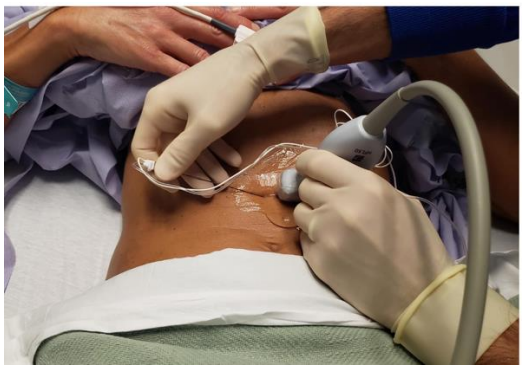
Figure 1. Example RSB Steps for Anesthesia Providers

LA Dose

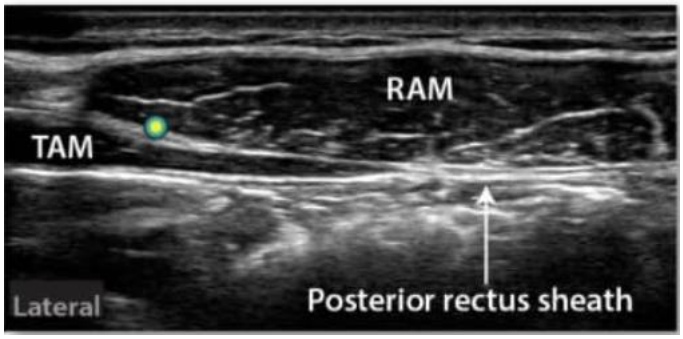
- 0.25% bupivacaine (with epinephrine 1:200 000) at 0.8 mL/kg
- Use half of the total volume per side

RSB Steps

1. Sterile prep and technique
2. With the patient in a supine position, place the linear (6-13 MHz) transducer in the transverse plane just above the umbilicus and center 1-2 cm off the midline.

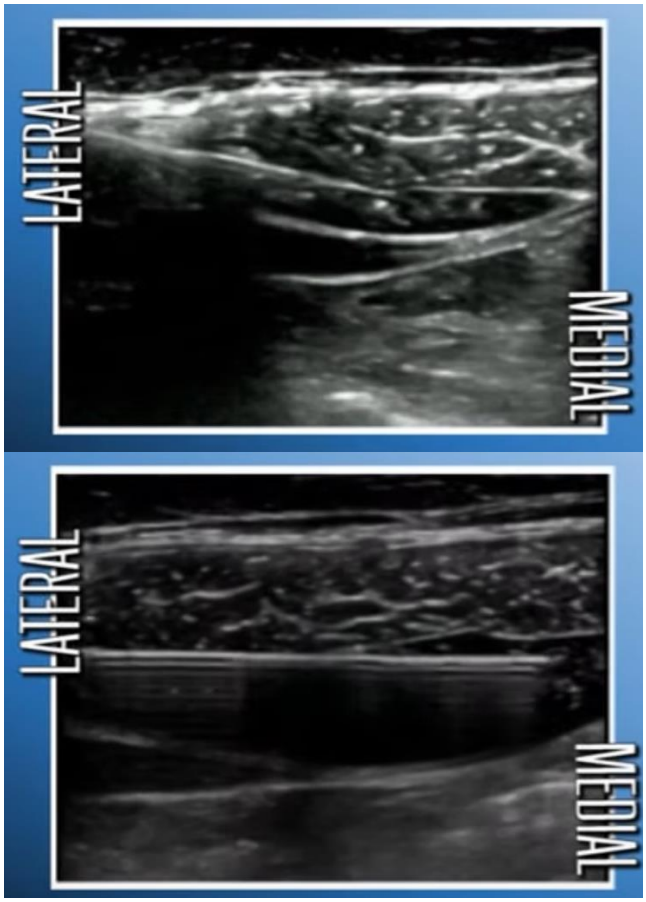


3. Identify the rectus abdominus muscle (RAM) which appears as a thick, lenticular-shaped muscle, and the posterior rectus sheath, a hyperechoic fascial covering deep to the muscle.
4. Adjust the probe laterally as required to identify the medial edge of the transverse abdominus muscle (TAM) deep to the rectus sheath.



5. Using an echogenic (50 mm/22-gauge often sufficient), advance needle in-plane with a lateral to medial approach aiming trajectory toward the lateral edge of the TAM

6. Once the needle tip is advanced posterior to the RAM and anterior to the posterior sheath hydro dissect with saline to confirm needle tip placement then can inject LA.



7. Repeat steps for the contralateral side.

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