STUDY PROPOSAL

A Comparison of Ultrasound Guided Transversus Abdominis Plane Nerve Block Technique Versus Laparoscopic Transversus Abdominis Plane Nerve Block Technique Versus Placebo on Postoperative Opioid Consumption for Major Colorectal Surgery

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STUDY OBJECTIVES

1. The primary objective of this study is to compare ultrasound-guided block of the transversus abdominis plane (TAP) vs. laparoscopic-guided TAP block, versus no TAP block on opioid consumption in the first 24 hours following colorectal surgery.
2. The secondary objective of this study is to assess the impact of these adjunctive regional techniques on overall patient satisfaction, postoperative pain scores, length of postoperative hospital stay, postoperative ileus, and adverse events directly related or unrelated to TAP block in the 30-day postoperative period.

BACKGROUND AND SIGNIFICANCE

Postoperative pain can pose significant challenges in the postoperative recovery of patients undergoing major colorectal surgery. Traditionally, opioids have played an important role in treating postoperative pain. It is well established that opioids are highly effective in relieving pain; however opioids are associated with numerous side effects that include nausea, vomiting, constipation, ileus, bladder dysfunction, respiratory depression, pruritus, drowsiness, sedation, and allergic reaction. These opioid side effects, which range in severity, can significantly interfere with discharge home following colorectal surgery. (1) Significant interest exists in the use of local anesthetic based regional anesthesia techniques as a means to extend the analgesic window for patients undergoing colorectal surgery (2). Specifically, the use of the TAP block as an adjunct in postoperative pain control has been widely reported in the anesthesia and colorectal surgery literature (2,3). Historically, the block was performed in a blind fashion with relative success and presently the block is typically performed either with ultrasound guidance or laparoscopic visualization (2,3). While TAP block has shown to be effective in post-operative pain control, the techniques used to place the block have not formally been compared.

We are purposing a prospective, patient-blinded, randomized study of patients undergoing major colorectal surgery to compare TAP block under ultrasound guidance versus laparoscopic visualization versus no TAP block. We hypothesize that laparoscopic-guided TAP block is non-inferior to ultrasound-guided TAP block with respect to perioperative pain control and either technique is superior to no TAP. In addition we will measure procedural time, any adverse events related to the block, overall postoperative analgesic requirement, analgesic duration, postoperative pain scores, length of postoperative hospital stay, incidence of postoperative ileus, and overall patient satisfaction between the three groups.

STUDY DESIGN

The proposed study is a patient-blinded, prospective randomized study to compare ultrasound-guided block of the TAP versus laparoscopic-guided TAP block versus no TAP block in patients undergoing major colorectal surgery. The primary outcome measure is analgesic requirement in morphine equivalents in the first 24 hours after surgery. Secondary outcome measures include overall postoperative analgesic requirement, postoperative pain scores, length of postoperative hospital stay, any adverse events related to TAP block, overall perioperative complications in the 30-day postoperative period and overall patient satisfaction after major colorectal surgery.

All groups will receive general anesthesia as the primary mode of anesthesia. Patients randomized to one of two treatment arms will also undergo either ultrasound-guided or laparoscopic-guided TAP block in the operating room at the conclusion of the procedure. Patients randomized to no TAP will not have a TAP block performed but will receive all routine intraoperative and postoperative analgesia as deemed appropriate by the anesthesia and primary surgical team. A standardized preoperative non-opioid pain regimen will be utilized. In the recovery room, short acting opioids for breakthrough pain will be available. Opioids will also be administered for rescue if need be. All patients will receive postoperative intravenous narcotics via patient controlled analgesia (PCA) device.

STUDY METHODS

I. Recruitment

a) Patients of the investigators will be recruited for this study during their preoperative outpatient appointments approximately one week before surgery. The study material packet containing the HIPAA and the informed consent form will be emailed to the patient for review. Thus the patient will have adequate time to ask questions and consider the study prior to scheduled surgery.
b) The patients will be contacted by one of the study investigators the morning of surgery at which time a signed consent will be obtained.
c) Only patients who have provided their written consent and indicated that they have been introduced to the study prior to meeting with the anesthesiologists on the day of surgery will be able to participate.
d) Screening procedures will make sure patients meet all inclusion criteria.

II. In the preoperative holding area:

a) An anesthesia investigator assigned to the specific case will assess patients and perform a pre-operative anesthesia assessment as per standard protocol at CSMC. None of this data will be recorded until written informed consent is obtained.
b) Patients will provide a detailed medical history including demographic information (e.g., age, weight, height, ethnic origin, smoking history, history of motion sickness, history of postoperative nausea and vomiting, as well as chronic analgesic usage). None of this data will be recorded until written informed consent is obtained.
c) Written informed consent will be obtained by one of the investigators.
d) Patients will be randomized in a blinded fashion by study staff to one of the groups via online randomization site, sealedenvelope.com, in a 2:2:1 fashion.

Group 1	n=100	Ultrasound guided TAP Block
Group 2	n=100	Laparoscopic guided TAP Block
Group 3	n=40	No TAP

III. During the intraoperative period

a) Standard anesthesia monitors will be applied: automatic blood pressure cuff, three-lead electrocardiography, capnography, and pulse oximetry will be used continuously.
b) Induction of general gnesthesia will be with propofol 2-3 mg/kg & a non-depolarizing muscle relaxant (choice will be operator dependent). Maintenance of anesthesia will be with an inhalational anesthetic.
c) The study staff performing randomization will instruct the anesthesiologist or surgeon to either block the transversus abdominis plane with ultrasound, laparoscopy, or no block.
d) For the block, a standard weight based dose (bupivacaine 0.25% with epinephrine 1:200,000, at a 1ml/kg dose) will be used for both ultrasound-guided or laparoscopic-guided block.
e) The block is administered between the costal margin and iliac crest in the anterior axillary line at 2 different sites on each side (4 injections total).
f) For ultrasound-guided TAP block, after the surgeons have completed their portion of the procedure, a member of the anesthesia research team will use sterile technique to prep the abdomen. The block is then placed bilaterally (at 2 different sites on each side of the abdomen) in the anterior axillary line, between the costal margin and iliac crest in the intermuscular plane between the internal oblique and transversus abdominis muscles using ultrasound guidance.
g) For laparoscopic-guided TAP block, the attending surgeon will perform the block at the conclusion of the procedure under laparoscopic guidance. Bilateral TAP block will be performed in the anterior axillary line between the costal margin and iliac crest. After the needle is passed through the skin, it is continued until 2 distinct “pops” are felt, indicating the needle pierced each of the 2 fascia layers (external oblique and internal oblique fascia).

After injection of the correct plane, a smooth raised area of fluid covered by transversus abdominis muscle is seen with the laparoscope. The laparoscopic vision also assures that the preperitoneal plane is not injected and that the injection does not go intraperitoneal.

h) Dose of anesthetics, analgesics, local anesthetics, and IV fluid therapy during the operation will be recorded in the anesthesia record as per standard procedure. A copy of the sonographic image will be collected for each patient at the conclusion of the block.

i) Duration of surgery (from skin incision until closure) and anesthesia (from induction of spinal until discontinuation of the anesthetic drug) will be recorded in the anesthesia record as per standard procedure.

IV. PACU

a) Verbal rating scale (VRS) for pain will be assessed by the PACU RN upon arrival to recovery room, then every 30min interval until discharge.
   - Requirements for "rescue" analgesic medication will be recorded before discharge.

b) Any adverse events during the perioperative period will also be noted by PACU RN.

V. Following completion of surgery (post-operative):

a) Anesthesia will be discontinued at skin closure.

b) Patients will be transferred to the recovery room after emergence from sedation

c) Treatment of surgical pain prior to discharge from the recovery room: moderate-to-severe pain (VRS > 7): hydromorphone, 1-1.5 mg IV, moderate pain (VRS of 4-6): hydromorphone 0.5 - 1 mg IV., mild pain (VRS 2-3), hydromorphone 0.1-0.2 mg IV. Patient pain control medication will continue with the initial treatment medication for all subsequent rescue doses as needed until recovery room discharge.

d) Patient nausea, vomiting, or retching will be initially treated with ondansetron 4mg IV. Patients unresponsive to ondansetron will receive metoclopramide 10mg IV.

e) Patient discharge criteria from PACU will include: awake and alert, and has stable vital signs.

VI. Patient evaluation during hospital admission:

- VRS for pain assessment will be utilized to assess pain within the first 72 hours postoperatively and pain scores will be recorded in the patient chart by the nursing staff as per routine CSMC protocol. The average pain scores will be calculated for study analysis.
- VRS scores along with dose for all opioids will be recorded.
- Physical signs and symptoms related to the peripheral nerve block (residual sensory blockade) will be noted.

- Patient satisfaction with the overall technique will also be queried.

Pain evaluation recorded by nursing staff as per standard CSMC guidelines:

- At PACU every 30 minutes
- During admission: 12, 24, 48, and 72 hours postoperatively

Patient satisfaction with analgesia will be assessed at the time of hospital discharge or within 30 days postoperatively by telephone using a patient satisfaction survey:

Pain Management Satisfaction Survey

On a scale of 1-5, how satisfied were you with your postoperative pain management?

Very Unsatisfied	Somewhat Dissatisfied	Neutral	Somewhat Satisfied	Extremely Satisfied
1	2	3	4	5

1 = very unsatisfied.

5 = extremely satisfied.

Statistical Considerations

The following data will be analyzed:

I. Data to be collected will include the following:
   a. Demographic details (age, gender, ethnicity, height, weight and BMI)
   b. Physical factors (height, weight, body mass index)
   c. American Society of Anesthesiologists Classification
      i. I – Healthy patient
      ii. II – Patient with controlled co-existing disease(s)
      iii. III – Patient with non-controlled co-existing disease(s)
      iv. IV – Patient with co-morbid condition(s) that are a constant threat to life
      v. V – Patient not expected to survive surgery

Data Analysis

Primary outcome measure:
With a sample size of 100 in each TAP block arm, a two group 0.025 one-sided t-test will have 80% power to reject the null hypothesis that the two groups are not equivalent in morphine (mg) use in the first 24 hours after surgery and rule in favor of the alternative hypothesis that the mean morphine use in the first 24 hours after surgery is equivalent for the two groups or the difference in means ($\mu_T - \mu_S$) is 10 or farther from zero in the same direction, assuming that the expected difference in means is 0 and the common standard deviation is 25**.**

Two group t-test of equivalence in means (equal n's)

	1
Test significance level, α (one-sided)	0.025
Equivalence limit difference, Δ_0	10.000
Expected difference, Δ_1	0.000
$\Delta_0 - \Delta_1$	10.000
Common standard deviation, σ	25.000
Effect size, $\delta = \lvert\Delta_0 - \Delta_1\rvert / \sigma$	0.400
Power (%)	80
n per group	100

Secondary outcome measure:
To show superiority of TAP to No TAP a two group t-test with a 0.05 two-sided significance level will have 88% power to detect the difference between a Control Group 1 (No TAP block) mean, μ_1, of 60 mg morphine use in the first 24 hours after surgery and a Group 2 (TAP block) mean, μ_2, of 45 mg morphine, a difference in means of 15, assuming that the common standard deviation is 25 mg, when the sample sizes in the two groups are 40 and 100, respectively.

Thus total number of patients to show non-inferiority between ultrasound-guided and laparoscopic-guided TAP block, and superiority of either technique to no TAP is 240 patients. Allowing for a 5% drop out rate (n=12 patients), the total number of patients we anticipate to recruit is 252.

SUBJECT RECRUITMENT

1. The subjects will be approached regarding the study during their preoperative consultation visit. If patient indicates a willingness to participate and meets the inclusion criteria and does not meet any exclusion criteria, they will be handed, emailed, or mailed a copy of the consent form to read, and the study will be scheduled at least 24 hours after they have received the consent form to review. The consent form will detail the purposes,

procedures, possible risks and benefits of the study. The informed consent form will have a contact number for the investigators to allow subjects to ask questions prior to the day of surgery.
2. Subjects must give informed consent to participate in the study.
3. When the patient arrives for the surgery, a study investigator will meet with the patient and discuss the procedure in detail in the preoperative holding area, and provide another copy of the informed consent for the patient to review and sign.
4. After the patient has signed informed consent, they will be randomized to one of three study arms by the study staff.

INCLUSION CRITERIA

A total of 252 patients undergoing laparoscopic colorectal procedures
Willingness and ability to sign an informed consent document
No allergies to anesthetic or analgesic medications
ASA physical status Class I – III adults of either sex
Aged 18-90 years

EXCLUSION CRITERIA

Patients who demonstrate any one of the following will be excluded from the study:

1. Refusal to participate in the study
2. Age <18 or > 90 years
3. Contraindications to regional blockage including but not limited to:
    a. Patient refusal to regional blockade
    b. Infection at the site of needle insertion
    c. Systemic infection
    d. Bleeding diathesis or coagulopathy (as diagnosed by history or laboratory evaluation)

BENEFITS TO STUDY SUBJECTS

TAP block techniques are well described in patients undergoing colorectal surgery procedures and with demonstrable benefit with respect to narcotic sparing pain relief. The benefit for our participants will be that these techniques will demonstrate enhanced duration of analgesia, reduction in opioid intake and a concomitant reduction in side effects. All of this should improve patient satisfaction.

COMPENSATION: There is no compensation for study participants.

POTENTIAL RISKS: There are the following risks associated with this prospective observational study.

A. Local Anesthetics: Inadvertent intravascular injection with resultant local anesthetic toxicity could result. Direct visualization, frequent aspiration and inclusion of epinephrine as a marker; make the incidence of this very low. In the setting of an inadvertent intravascular injection, Intralipid is readily available and has been shown to be very effective in reducing morbidity and mortality from LAST (Local Anesthetic Systemic Toxicity).
B. Transversus abdominis plane block. Inadvertent intravascular injection is a potential risk associated with any regional technique. This is seen in less than 0.01% of patients and that percentage is further mitigated with direct visualization under ultrasound guidance.
C. Epinephrine 1:200,000 produce a minimal risk of vasoconstriction (it is used as a marker to reduce the incidence of inadvertent intravascular injection).
D. Injection site hematoma, ecchymosis, bleeding. Ultrasound guidance and laparoscopic guidance will allow investigators visualization to avoid puncture of blood vessels and subsequent hematoma. Patients with known bleeding diathesis or those on therapeutic anticoagulation will be excluded from the study.
E. Injection site infection. Sterile technique will minimize this complication. Investigators will monitor the injection site for signs of infection including erythema, drainage, pain, tenderness or fluctuance.
F. Pain at the injection site. Small needles are use to perform the injection and therefore minimizing associated pain at the injection site.

MAINTAINANCE OF CONFIDENTIALITY: Patients' names will not be divulged and all data will be coded in the study records. Information gained during the course of the study will only be used by the investigators for the purpose of this study and no patient names or other identifying data will be used in any future publications.

PROCEDURES TO MAINTAIN CONFIDENTIALITY

All data will be coded and patient's name will not be disclosed in any of the study records according to standard HIPAA policy. All the information gained during the course of the study will be used by the investigator for the evaluation of the purpose of this study in patients

undergoing outpatient surgery. No patient names (or other identifying data) will be used in any further publication.

DATA ACCURACY AND PROTOCOL COMPLIANCE

1. Obtaining Informed Consent: A study investigator will first insure subject eligibility, and upon confirmation of this, obtain informed consent from the subject in an interview. Assurance of "informed" consent will be performed by discussing the study with the subject, and providing the patient a copy of the consent form.

2. Maintaining Confidentiality: Once enrolled in this study, each participating subject will be assigned a unique numerical identifier, with all other identifying information removed. Subjects' names will not be divulged and all data will be coded in the study records. A master list of enrolled subjects will be kept in a locked and secure room, in a locked and secure building, directly accessible only by the study investigators. Authorized research personnel access to any identifying information will be restricted to the minimal level needed for performance of the study. No patient names (or other identifying data) will be used in any future publication(s).

3. Quality Control for Data Accuracy:
    a. Subject eligibility: Each potentially eligible subject referred to the study will first undergo evaluation by a study investigator regarding whether patient meets inclusion criteria and any exclusion criteria. This will be done with direct referring physician interview, direct subject interview, and focused medical record review.
    b. Subject demographic data and questionnaire: Collected by study investigator through direct subject interview and focused medical record review.
    c. Laboratory samples: None will be collected

REFERENCES

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