STUDY PROTOCOL

A prospective randomized trial of Transversus abdominis plane (TAP) Intraoperative block with bupivacaine/dexamethasone aGainst Liposomal bupivacaine (Exparel®): the TINGLE trial

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PRINCIPLE INVESTIGATOR

Karen Zaghiyan, M.D.*

CO-INVESTIGATORS

Philip Fleshner, M.D.*

Adam Truong, M.D.**

Rita Shane, PharmD***

Hai Tran, PharmD***

INSTITUTION
Cedars-Sinai Medical Center
8700 Beverly Blvd.
*Division of Colorectal Surgery
**Department of Surgery
***Department of Pharmacy

CONTACT INFORMATION:
ADDRESS:
8737 Beverly Blvd, Suite 101
Los Angeles, California 90048
PHONE: 310-289-9224
FAX: 310-289-8995
E-MAIL: karen.zaghiyan@cshs.org

STUDY OBJECTIVES

1. The primary objective of this study is to prospectively evaluate post-operative opioid use in the first 48 hours after minimally invasive colorectal surgery who received either a bupivacaine/epinephrine/dexamethasone vs. liposomal bupivacaine (Exparel) laparoscopic-guided transversus abdominis plane (TAP) block.
2. The secondary objectives of this study are to assess the impact of these adjunctive regional techniques on postoperative pain scores, time until ambulation, antiemetic use, 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, particularly following colorectal surgery. (1) Significant interest has grown for the use of guided regional anesthesia, specifically the use of the transversus abdominis plane (TAP) block to extend the post-operative analgesic window and ultimately limit opioid use (2-3). Traditionally, bupivacaine with or without adjuncts such as epinephrine or steroids was the long-lasting amide local anesthetic of choice for TAP block injections. While bupivacaine formulations including a steroid has been shown to prolong the anesthetic effects of the regional field block (4), a new liposomal-depo formulation of bupivacaine (Exparel) has gained popularity and has additionally been shown to provide extended analgesia (5). Although promising data exists surrounding each modality, liposomal bupivacaine has not been studied in a well-powered clinical trial specifically in colorectal patients nor compared to a bupivacaine/steroid mixture.

We are proposing a prospective randomized study of patients undergoing major laparoscopic colorectal surgery to compare the analgesic effects of a bupivacaine/epinephrine/steroid mixture versus liposomal bupivacaine (Exparel). We hypothesize that the liposomal formulation of bupivacaine will provide superior perioperative pain control at 48 hours post-operation measured by total consumed oral morphine equivalents. In addition, we will measure postoperative pain scores, time until ambulation, antiemetic use, length of postoperative hospital stay, postoperative ileus, and adverse events directly related or unrelated to TAP block in the 30-day postoperative period between the three groups.

STUDY DESIGN

The proposed study is a prospective randomized study to compare two TAP blocks treatment arms:

1. bupivacaine with epinephrine and dexamethasone
2. liposomal bupivacaine (Exparel)

in patients undergoing major laparoscopic colorectal surgery. The primary outcome measure is analgesic requirement in oral morphine equivalents in the first 48 hours after surgery. Secondary outcome measures include postoperative analgesic requirements at various time points (within the post-anesthesia care unit, at 24 hours postop, and 72 hours postop), total opioid requirements, antiemetic requirements, postoperative pain scores, length of postoperative hospital stay, any treatment-associated adverse events related to the TAP block, and overall perioperative complications in the 30-day postoperative period after major colorectal surgery.

All groups will be counseled and asked to consent for the study at the time of their preoperative clinic visit and copy of the protocol will be provided to them. Patients undergoing laparoscopic major colorectal surgery will receive general anesthesia as the primary mode of anesthesia. A standardized preoperative non-opioid pain regimen will be utilized. Both groups will receive all routine intraoperative and postoperative analgesia as deemed appropriate by the anesthesia and primary surgical team. All patients will be prescribed scheduled non-opioid analgesics with available oral and intravenous narcotics for breakthrough pain postoperatively. The current standard of care includes a multimodal approach to pain control including the utilization of a regional field block in an effort to improve pain control and decrease postoperative opioid use. The choice of local anesthetic medication administered within the TAP block is proceduralist-dependent and variable. A wide range of medications have been utilized including bupivacaine formulations with epinephrine and dexamethasone and a long-acting sustained-release liposomal bupivacaine formulation to increase the block effects or duration. Each are considered within the standard of care and have been studied independently showing improved postoperative pain control (6); however, these two formulations have not been studied against each other to determine superiority. We propose a prospective randomized study to comparing TAP blocks with injected bupivacaine/epinephrine/dexamethasone versus liposomal bupivacaine in patients undergoing major laparoscopic colorectal surgery.

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) No emails soliciting patients outside of the outpatient clinic setting will be conducted.
c) The patients will be contacted by the study investigators the morning of surgery at which time a signed consent will be obtained.
d) 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.
e) Screening during each step of the recruitment process will ensure patients comply with inclusion and exclusion criteria.

II. In the preoperative holding area:

a) 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.
b) Standard of care multimodal analgesia medications will be administered including:
    a. Acetaminophen oral 1000 mg
    b. Celecoxib oral 200 mg
    c. Gabapentin oral 600 mg (300 mg for patients over age 65)
    d. Heparin 5000 units sq
    e. Scopolamine patch 1.5 TD (for patients < age 65)
    f. Intravenous fluids (lactated ringers at 30 ml/hr)
    g. Additional analgesics may be given as needed.
c) Written informed consent will be obtained by one of the investigators.

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) Choice of intraoperative anesthesia drugs will be per attending anesthesiologist preference except the addition of our standard colorectal enhanced recovery protocol which will be applied to all:
    a. Dexamethasone 4 mg IV x 1
    b. Metoclopramide 10 mg IV x 1
    c. Ketorolac 30 mg IV x 1 (15 mg in patients >65 y.o., renal impairment or weighing <50 kg)
    d. Lidocaine 2mg/kg/hr infusion (Hold for age >65, cardiac arrhythmia, Congestive heart failure (CHF), Chronic obstructive airway disease, beta-blocker use, alpha-agonist use, abnormal electrolytes, or liver impairment)
    e. Magnesium IV bolus 30mg/kg (over 30 minutes) then 6mg/kg/hr (Hold for age >65 y.o., cardiac arrhythmia, history of heart attack, CHF, renal impairment (SCr >1.5)

        Lactated ringers at 8ml/kg/hr unless blood loss >300cc or converted to open surgery

c) Immediately after the final laparoscopic portion and before evacuation of pneumoperitoneum, the patient will undergo randomization by one of the study staff (AT) via sealedenvelope.com random number generator.
    a. If the patient underwent a conversion from laparoscopic to open surgery, they will not be randomized
d) The study staff performing randomization (AT) will instruct the surgical technologist and circulating nurse to prepare the medication formulation of the matched study arm: either bupivacaine/epinephrine/dexamethasone or liposomal bupivacaine. This will be done while the surgeon/ block administrator are outside of the operating room.
e) For the bupivacaine/epinephrine/dexamethasone treatment arm, a standard weight-based dose will be used. A 1 ml/kg dose of 50:50 mix of 1) bupivacaine 0.25% with epinephrine (1:200,000) and 2) bupivacaine 0.25% without epinephrine will be combined with 8mg (4mg/ml) dexamethasone.
f) For the liposomal bupivacaine treatment arm, a dosing regimen as recommended on the package insert will be used. 20 ml of 133 mg/10ml (totaling 266 mg) liposomal bupivacaine (Exparel) solution will be mixed with 0.5% bupivacaine without epinephrine totaling a 1 ml/kg weight-based volume. The maximum volume of 0.5% bupivacaine co-administered with liposomal bupivacaine is 30ml or 150 mg and will not exceed a 1:2 ratio of milligram dose of bupivacaine HCl to liposomal bupivacaine. Note, liposomal bupivacaine contains 266 mg of free base bupivacaine which is the molar equivalent to 300 mg bupivacaine HCl. Thus, a 1:2 ratio would entail a maximum co-administered dose of 150 mg or 30 ml

0.5% bupivacaine without epinephrine. For patients heavier than 50 kg, saline will be added to dilute the mixture and expand the volume to 1ml/kg total volume.

g) Groups are summarized below:

Group 1	n=50	Bupivacaine with epinephrine and dexamethasone
Group 2	n=50	Liposomal bupivacaine

h) The bilateral laparoscopic-guided 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. The block is administered at 2 different sites on each side (4 injections total).

i) Dose of anesthetics, analgesics, local anesthetics, and IV fluid therapy during the operation will be recorded in the anesthesia record as per standard procedure.

j) Duration of surgery (from skin incision until closure) and anesthesia will be recorded in the anesthesia record as per standard procedure.

k) Total opioids received will begin recording from when skin closure begins.

IV. PACU

a) Per standard care, verbal rating scale (VRS) for pain will be assessed by the PACU RN upon arrival to recovery room, as needed while in PACU, and then before discharge from the PACU.

b) Narcotic usage will be tracked through PACU as a separate category

c) Requirements for "rescue" analgesic medication will be recorded before discharge.

d) 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 per Standard Care:

i. Mild pain (VRS 1-3): No rescue pain medications will be administered

ii. Moderate pain (VRS 4-6): tramadol 5 mg oral or hydromorphone 0.2 mg IVP every two hours if unable to tolerate oral

iii. Severe pain (VRS 7-10): tramadol 10 mg oral or hydromorphone 0.5 mg IVP every two hours if unable to tolerate oral

d) Patient nausea, vomiting, or retching will be initially treated metoclopramide 10 mg IV. Patients unresponsive to this will be given ondansetron 4 mg IV and prochlorperazine 10 mg IV if still ineffective, per standard care.
e) Patient discharge criteria from PACU will include: awake and alert, and stable vital signs.
f) Postoperative enhanced recovery pathway will be initiated and multimodal analgesia will be ordered per our standard practice for all patients:
    i. Regular diet + Boost TID starting POD 0
    ii. Heparin 5000 units SQ TID starting POD 0
    iii. Ambulation TID will be encouraged beginning POD 0
    iv. Gabapentin l60 mg po QHS or 300 mg po qHS for patients over age 65
    v. Acetaminophen 1000 mg oral every 8 hours
    vi. Celecoxib 200 mg oral bid
    vii. Breakthrough pain will be controlled as follows:
        1. Mild pain (VRS 1-3): No rescue pain medications will be administered
        2. Moderate pain (VRS 4-6): tramadol 5 mg oral or hydromorphone 0.2 mg IVP every two hours if unable to tolerate oral
        3. Severe pain (VRS7-10): tramadol 10 mg oral or hydromorphone 0.5 mg IVP every two hours if unable to tolerate oral
        4. Patients having pain further uncontrolled by above methods will be allowed to deviate from protocol to achieve satisfactory pain control deemed appropriate by treating physicians including but not limited to use of oral oxycodone, intravenous acetaminophen, ketorolac, patient controlled analgesia, and repeat of TAP block or epidural analgesia
        5. Patients matched in both control and experimental arms who require a repeat TAP block or epidural anesthesia to achieve satisfactory pain control will remain in their previously designated study group and will undergo to intention-to-treat analysis.

VI. Patient evaluation during hospital admission and up to 1 week postop:
    a) VRS for pain assessment will be utilized to assess pain within the first 72 hours postoperatively, per standard care, 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.
    b) VRS scores along with dose and administration time for all opioids will be recorded, per standard care.

c) Pain evaluation recorded by nursing staff as per standard CSMC guidelines:
    a) Within the PACU as needed.
    b) During admission: 12, 24, 48, and 72 hours postoperatively and as needed.
d) Antiemetic usage will be recorded
e) Return of bowel function
    a) For patients with bowel continuity: time till flatus and BM will be measured by morning inquiry or stool production
    b) For patients with ostomy/ diversion: time till obvious visual gas filling of the bag or ostomy production of succus beyond 20 ml / day
f) Ambulation
    a) Defined as walking >50 feet out of the patient room
g) Physical signs and symptoms related to the peripheral nerve block (residual sensory blockade) will be noted.

VII. Post-Discharge

a) If patient is discharged before 72 hours, they will be called by study team member and asked about their narcotic usage and timing and total narcotic use at 72 hours will be calculated
b) If unable to be reached within 24-48 hours, they will be queried at their post-operative visit.

VIII. Adverse events

a) If patient was converted from laparoscopic to open surgery, they will not meet criteria for randomization
b) If a patient is readmitted to the emergency department or the inpatient hospital post-discharge within 30 days, the Clavien-Dindo classification (7), circumstances, cause, and possible associations to treatment intervention will be recorded.
c) If a patient leaves against medical advice, they will be classified as "lost to follow-up."
d) The patient will be assessed in clinic at 30 days to evaluate any adverse events during this time.

Statistical Considerations

The following data will be analyzed:

I. Data to be collected will include the following:
    a. Demographic details
        i. Age
        ii. Gender

iii. Ethnicity
iv. Smoking/alcohol use
v. Narcotic use

b. Physical factors
i. Height
ii. Weight
iii. Body mass index

c. Medical history -
i. Charlson comorbidity index (8)

d. 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

e. Operative factors
i. Operative indication
ii. Operation received
iii. Conversion to open surgery
iv. Operation time
v. Incision length will be measured and tabulated by surgeon
vi. Number of laparoscopic ports

f. Treatment received

g. Outcomes
i. Narcotic usage
ii. Pain scale
iii. Time till flatus/ bowel movement
iv. Foley removal
v. Ambulation
vi. Hospital length of stay
vii. Adverse events
viii. Hospital readmission

Data Analysis

Sample size calculation:
With a sample size of 50 patients in each arm, a two group 0.05 two-sided t-test will have 80% power to reject the null hypothesis that the two groups are equivalent in morphine (mg)

use in the first 48 hours after surgery and rule in favor of the alternative hypothesis that the mean morphine use in the first 48 hours after surgery is different for the two groups, assuming that the expected difference in means is 50% and the common standard deviation is 25**.**

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

Test significance level, p (two-sided)	0.05
Expected difference, Δ	15.000
Expected standard deviation, s	25.000
Power (%)	80
n per group	50

Randomization will be conducted 1:1, yielding 50 patients in each TAP block arm, totaling 100 patients. Block randomization in random blocks of 4 and 8 will be performed to assure equal group sizes.

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 phone number/ email address 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, and after the possibility of conversion to open surgery has been excluded intraoperatively, they will be randomized to one of two study arms by the study staff.

INCLUSION CRITERIA

1. Male or Female
2. Undergoing major laparoscopic colorectal procedure
3. Willingness and ability to sign an informed consent document

4. No allergies to anesthetic or analgesic medications
5. ASA physical status Class I – III
6. 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. Pregnancy
4. Contraindications to regional anesthetic including but not limited to:
    a. Patient refusal to regional field blockade
    b. Allergy
    c. Infection at the site of needle insertion
    d. Systemic infection
    e. Bleeding diathesis or coagulopathy (as diagnosed by history or laboratory evaluation)
    f. Liver or renal disease (SCr > 1.5)
5. Chronic opioid use

ANTICIPATED COSTS

The study will be conducted within standard of care practices. The patient cost of participation can be equated to associated standard medical costs that will be billed to medical insurance as routine practice. Each treatment arm differs in the type of medication administered in the TAP block. Exparel will be provided free of charge to patients assigned to that treatment arm. Pharmacy has agreed to manually suppress this charge from the hospital billing. Patients who receive the low cost bupivacaine/epinephrine/dexamethasone medication will be billed as per standard hospital protocol.

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 the determination of superior regional block agents to enhance duration of analgesia and reduce opioid intake together with its side effects. All of this should improve patient satisfaction and potentially facilitate an expeditious hospital discharge.

COMPENSATION: There will be 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, cardiac arrhythmia and arrest may result. Intralipid is readily available and has been shown to be very effective in reducing morbidity and mortality from LAST (Local Anesthetic Systemic Toxicity).
B. Liposomal bupivacaine (Exparel): The side effect profile of liposomal bupivacaine has been studied in 6 controlled phase I-III trials and has been shown to be similar in safety and side effect profile to bupivacaine HCl and normal saline (9).
C. Bupivacaine/epinephrine/dexamethasone: While large randomized clinical trials do not exist for the mixture, it is regarded as safe. Multiple studies have reported safety in humans and rats for perineural injection (10-12).
D. 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 laparoscopic guidance.
E. Epinephrine 1:200,000 produce a minimal risk of vasoconstriction (it is used as a marker to reduce the incidence of inadvertent intravascular injection).
F. Injection site hematoma, ecchymosis, bleeding. 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.
G. 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.
H. Pain at the injection site. Small needles are used to perform the injection and therefore minimize associated pain at the injection site.
I. Chronic liver or renal disease may alter the metabolism of amide anesthetics. Due to this, patients with these chronic conditions will be excluded from the study.
J. There is a potential risk of a breach of confidentiality if unauthorized persons accidentally view subjects' medical records containing private and identifiable information

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

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