1) Protocol Title

Transversus abdominus plane (TAP) block catheters vs liposomal bupivacaine for pain control after colorectal surgery: A prospective randomized control trial

Protocol Version Date: *1/31/17*

2) Objectives

i) Primary: Compare the use of TAP blocks with ropivicaine bolus and ropivicaine catheters versus single shot TAP blocks with liposomal bupivacaine

(1) We anticipate superior efficacy and pain control with liposomal bupivacaine TAP blocks measured by use of opioids (measured in oral morphine equivalents) in the first 48 hours following surgery.

ii) Secondary:

(1) Assess the efficacy and safety of TAP blocks for pain control after colorectal surgery in a prospective fashion

(a) Hypothesis: Anticipate satisfactory pain control in both TAP block groups for somatic abdominal pain measured as proportion of pain scores in the mild range (up to 4 out of 10 pain documented in nursing notes)

(b) Anticipate equivalent side effects measured as duration of ileus, rash, itching, nausea/vomiting.

(2) Compare the pharmacological costs and medical utilization costs of TAP block catheters versus single shot injection of TAP block with liposomal bupivacaine

(a) Anticipate lower medical utilization costs with single shot injection with liposomal bupivacaine TAP blocks

(b) Measured as acquisition cost of drugs and supplies

3) Background

Pain control after abdominal laparoscopic surgery involves multiple components of somatic and visceral pain. Although opioids are commonly used for acute postoperative pain control, opioid – induced constipation that can increase the risk of postoperative ileus, nausea, and pruritus are significant side effects that may prolong hospital length of stay. Multimodal analgesic regimens have been shown to increase pain control while sparing the use of systemic opioids. These have included modalities such as acetaminophen, non-steroidal anti-inflammatory drugs, and peripheral nerve blocks.

The transversus abdominus plane block (TAP) is a minimally invasive ultrasound guided peripheral nerve block that is helpful in decreasing somatic abdominal pain after surgery

and decreases opioid consumption while improving pain control. TAP involves local anesthetic infiltration between the internal oblique and the transversus abdominis plane in which space the terminal branches of the anterior roots of the lower six thoracic and first lumbar nerves course. These nerves innervate the anterolateral abdominal wall. In colorectal surgery patients, TAP have resulted in a decrease in 24-hour morphine consumption as well as earlier discharge and return to diet time compared to patient controlled analgesia (PCA).

At UC Davis, it is standard practice to place TAP blocks with catheters for adult colorectal surgery patients for perioperative pain control. In many cases, the TAP catheters will remain in the patient for two days and are removed when the patient's somatic pain is controlled and they able to tolerate oral intake. However, it is resource intensive requiring the use of two sterile peripheral nerve catheter kits, two CADD infusion pumps, nursing time to replace the ropivicaine infusion cassette every 8-10 hours, and 30-40 minutes of physician time for block placement with additional physician time needed for ongoing catheter management. There is also a risk of catheter – related complications including inadvertent dislodgement, catheter infections, and increased burden to the patient from the two additional catheters tethered to the patient.

An alternative TAP can be performed using liposomal bupivacaine (Exparel). This is an extended release local anesthetic that has been shown to last 48-72 hours and is FDA approved for surgical plane infiltration including TAP blocks, as detailed in a 2015 FDA letter. Although the expense of the Exparel is higher than a vial of ropivicaine, it is not clear that patients will receive equivalent pain control and satisfaction with one time Exparel TAP blocks as compared to TAP catheters with ropivicaine for the first 48-72 hours. Further, the costs and medical utilization related to TAP catheters may be greater than that of one vial of Exparel used for TAP blocks. Although there have been smaller studies showing the efficacy of Exparel for TAP blocks, there is currently no prospective study that evaluates the efficacy of single injection TAP blocks with Exparel compared to ropivicaine TAP catheters for colorectal surgery patients.

This study is designed to assess the comparative efficacy and cost of these two approaches. Results from this study will be significant to the fields of anesthesiology, acute pain management and colorectal surgery. With this prospective study, we will have concrete data on the use of single shot Exparel TAP blocks and TAP catheters to improve patient care at UC Davis and educate other institutions.

References:

Feierman, Dennis E., et al. "Liposomal bupivacaine infiltration into the transversus abdominis plane for postsurgical analgesia in open abdominal umbilical hernia repair: results from a cohort of 13 patients." *Journal of pain research* 7 (2014): 477.

McDonnell JG, O'Donnell B, Curley G et al. The analgesic efficacy of transversus abdominis plane block after abdominal surgery: a prospective randomized controlled trial. Anesth Analg 2007; 104: 193–197.

Siddiqui MR, Sajid MS, Uncles DR et al. A meta-analysis on the clinical effectiveness of transversus abdominis plane block. J Clin Anesth 2011; 23: 7–14.

Walter, Catherine J., et al. "A randomised controlled trial of the efficacy of ultrasound-guided transversus abdominis plane (TAP) block in laparoscopic colorectal surgery." Surgical endoscopy 27.7 (2013): 2366-2372.

Zafar N, Davies R, Greenslade GL, Dixon AR. The evolution of analgesia in an 'accelerated' recovery programme for resectional laparoscopic colorectal surgery with anastomosis. Colorectal Dis 2008; 12: 119–124.

4) Inclusion and Exclusion Criteria

Criteria for inclusion will be patients over 18 years of age presenting for elective colorectal surgery with Dr. Linda Farkas, Division of Colorectal Surgery, Department of Surgery.

Individuals under 18 years of age or above the age of 90, pregnant women, prisoners and patients unable to provide consent, and patients unable to speak English will be excluded. If the patient is on systemic anticoagulation and is at an increased risk of hematoma then they will be excluded as the block will not be performed. Patients with an allergy to a local anesthetic will also be excluded.

5) Study Timelines

Eligible patients will be approached for research and written informed consent will be collected on the day of surgery. TAP block catheters or single shot liposomal bupivacaine TAP blocks will be placed in the preoperative holding area, prior to surgery start. Intraoperative and post-operative care will be routine at the discretion of the physicians caring for the patient. TAP block catheters are followed by the acute pain service faculty until removal of the catheters, typically post operative day two or three.

We anticipate completing our enrollment in 2 years (24 months), with data analysis completed within 6 months after the final patient has been enrolled.

6) Study Endpoints

The primary end point will be after enrollment of patients is complete for both the TAP catheter group and the liposomal bupivacaine group. Secondary endpoints are the time for PACU discharge and discharge from the hospital.

7) Procedures Involved

Individuals will be screened for study inclusion/exclusion criteria in the preoperative holding area. Faculty anesthesiologist, resident anesthesiologist or trained research staff will approach eligible patients in the preoperative holding area, explain the study, and obtain written informed consent.

Consenting patients will be randomized to a study arm (Exparel single injection TAP block or TAP block catheter). Randomization will be performed based on a random number generator (1 or 2) and after patient is consented. Group 1 will be deemed the Exparel single shot group while Group 2 is the TAP catheter group. Both procedures are performed by the acute pain service with an anesthesiology faculty member and an anesthesiology resident on the rotation that month under direct supervision. When patients are enrolled into the study, the TAP block for both arms will be performed in the preoperative holding area, prior to induction of general anesthesia. Prior to any procedure, a preoperative evaluation is performed, consent is verified, procedural time out is performed, and emergency medications are available if there are signs of local anesthetic toxicity. For each patient, maximum allowable doses of local anesthetic will be calculated as to avoid the risk of any possible local anesthetic overdose.

The Exparel TAP block dose will be provided by inpatient pharmacy and will consist of 266 mg of Exparel (1.3% in 20cc) diluted to 60 ml total volume with 40 ml of preservative free normal saline. An injection of 30 ml of volume will be performed on each side, with a total of 60ml for bilateral TAP blocks. Exparel is currently FDA approved for surgical site infiltration and the classification of TAP blocks as surgical field blocks was specified in a FDA letter in fall 2015. This is the current standard dilution and volume used in other academic centers for Exparel TAP blocks.

For those randomized to the TAP catheter group, 30 ml of 0.5% ropivicaine will be diluted with an additional 30 ml of preservative free normal saline for a total volume of 60cc, with 30 ml injected into each side. We will also place peripheral nerve catheters, approximately 3-5cm into the TAP space after injection of the ropivicaine solution. Catheters will be secured to the skin with tegaderm tape. Infusions will be ordered with CADD pumps and will be initiated at a rate of 8 ml/hr of 0.2% ropivicaine on the inpatient floor.

Postoperatively, patients will be monitored in the PACU per routine care. Patients will be ordered a combination of standardized short acting opioids (fentanyl), and long acting opioids (hydromorphone) in additional to anti-emetics (ondansetron 4mg IV) for administration if needed in the PACU. In the PACU, perioperative nursing staff will dose medications accordingly to the EMR orders and the PACU clearance time will be logged as well. PACU duration is calculated as the time interval between patient arrival into the PACU and when the patient is signed out of the PACU by the PACU anesthesiology resident/faculty.

Post-PACU hospital course will proceed as is standard of care with PRN pain medication. Patient with single shot Exparel TAP blocks will be seen on the inpatient floor for two days after the surgery to assess for postoperative pain control. Patients with TAP catheters will also be seen daily until the catheters are removed by the acute pain service and when the patient is tolerating an oral diet and there are no overt signs of postoperative ileus. Standard hospital discharge criteria will be used for both groups.

Information will be collected from the patients' hospital stays, including Ultrasound imaging of the patient's TAP block, intraoperative anesthesia record, the amount of opioid use in morphine oral equivalents in the first 6, 12, 18, and 24, 36, and 48 hours after surgery, incidence of nausea/vomiting, pain score averages from EMR Epic RN Pain data, PACU clearance time and length of hospital stay.

8) Data and/or Specimen Management and Confidentiality

During the study phase, patient information will be stored electronically via a password protected database on the UC Davis OneDrive cloud storage folder. Only authorized study staff will have access to the file while access to the UC Davis OneDrive folder requires UC Davis login. Patients' information will be stored on a secure database with indirect identifiers, such as patient 1, patient 2, etc. There will be a separate password protected document that contains the indirect and direct identifiers to match the two. After the study has been closed, consents will be maintained for three years, and HIPAA consents for six years, in compliance with IRB rules and regulations. Any data obtained from the Electronic Medical Record (EMR) will be identified by subject ID only and collected onto an encrypted spreadsheet on the PI's password protected computer.

Statistical analysis plan & Sample size calculation

The primary outcome measure will be the between group difference in opioid consumption in the first 48 hours surgery.

We anticipate superior pain control in the Exparel group based on the potential for TAP catheter problems such as catheter dislodgement and lack of timely infusion refill. A difference in 20% of opioid oral morphine equivalents will be considered clinically significant. Prior reports (Carney et al) suggest a difference of 55.3mg ± 17.6 in the control group versus 26.8mg ± 19.8 in the TAP block group. Using a power of 0.8 and $p<0.05$ as statistically significant yields a sample size of 44 per group to show significance. We will enroll 100 to allow for early withdrawal or protocol violations, with planned interim analysis at n=20 of each group completing the study (40 patients) to allow sample size refinement as needed. Data will be analyzed for normal distribution. Normally distributed data will be compared using a T-test for the 2 groups; data that is not normally distributed will be compared using the Mann Whitney U test. Categorical data will be compared by Chi square.

All data will be stored online in the secure UC Davis OneDrive folder with password protected files. All research staff will have completed HIPAA – related training and IRB – related training.

9) Provisions to Monitor the Data to Ensure the Safety of Subjects

Patients will be monitored closely in the PACU prior to discharge to the inpatient floor for any signs and symptoms of local anesthetic toxicity, abdominal pain, or allergic reaction. The dose of local anesthetic given will be calculated to be less than the toxic dose level for ropivicaine (2-3mg/kg) and liposomal bupivacaine (2-3mg/kg). Patients receiving TAP catheters will be seen daily by the acute pain service who will visually inspect the site of insertion and assess the patient for any abdominal pain.

Any adverse events, such as intravascular injection, allergic reaction, or other unanticipated event will be assessed for its causative relationship to the TAP block by the PI (Dr. Zhou).

If a serious adverse event occurs, it will be reported immediately to the IRB and will trigger an immediate suspension in enrollment and a review of the injection protocol with the Chiefs of both the Departments of Anesthesiology and Colorectal Surgery. If any performer error can be identified and corrected, then with approval from the departments enrollment will continue. If not, the study will be terminated.

Any unexpected adverse events will be documented and reported to the IRB as well as study participants.

We will cumulatively review the data after 20 subjects in each study arm have been enrolled, and then again at 50 patients, 75 patients, 100 patients until study completion. Data will be reviewed for any adverse effects from TAP blocks, pain scores, opioid consumptions, other additional secondary outcome measures such as nausea/vomiting.

10) Withdrawal of Subjects

Because this is a study comparing a single injection versus a peripheral nerve catheter, patients receiving a single injection are able to withdraw voluntarily any time prior to the injection. If there was difficulty with visualization of the TAP plane with ultrasound due to body habitus, then the patient will be withdrawn from the study. At all instances, patient safety will be the primary priority above all over study parameters.

With the TAP catheter group, patients may withdraw voluntarily from the study if they wish.

11) Risks to Subjects

A possible risk is the TAP block not providing adequate pain control postoperatively. Patients will have access to routine IV and oral pain medications including opioids, acetaminophen, NSAIDS, and other multimodal adjuncts. Complications after TAP blocks are rare, and there are no known reports of local anesthetic toxicity after TAP block injections. There have been case reports of liver laceration with inadvertent injury by the injection needle while performing TAP blocks. There is also one case report of catheter placement into the peritoneal cavity, although there was no injury to any organs. The likelihood of any needle placement errors is minimized by ultrasound visualization of the TAP plane and the needle. Any adverse event is less likely with careful aseptic technique, performance of a procedural time-out prior to the block, and careful aspiration prior to injection of any local anesthesic.

The use of Exparel has been shown to have no greater incidence of adverse events compared to plain bupivacaine based on 10 randomized control trials with 823 subjects comparing the two.

Allergic reactions/toxicity from local anesthetics are extremely rare, and symptoms can range from itching, swelling, difficulty breathing, abnormal heartbeat, and in extreme cases, death.

TAP catheters have an inherent risk of hematoma formation, dislodgement and infection due to the nature of having a foreign body catheter in the TAP plane of a patient.

12) Potential Benefits to Subjects

Patients may have decreased postoperative pain control with either of the TAP blocks. They may also have decreased intraoperative opioid use as well as less postoperative opioid utilization, which in addition to better pain control may lead to less opioid – related side effects including pruritus, decreased incidence of opioid related constipation and ileus, nausea and vomiting.

13) Sharing of Results with Subjects

No additional information will be shared with research subjects

14) Provisions to Protect the Privacy Interests of Subjects

Patients will be approached about enrolling in this study in the preoperative area. The person obtaining consent will be a research team member from Anesthesiology and/or Surgery departments. Patient beds in this area are one bed per room; therefore, the conversation will be in private, between the research staff and patient. Family members may be present, but this is standard for all preoperative consents (anesthesia consents, block consents, sometimes surgical consents if they are not on file). The consent process will specifically state that refusal to enroll will not result in any penalty, including any withholding of pain medication in the future. Post-operatively, patient privacy will be protected and only study personal will have access to the encrypted study database with patient data.

15) Compensation for Research-Related Injury

There is no specific compensation for study participation. TAP blocks are a billable procedure and used routinely for postoperative pain control in colorectal surgery patients. Any possible complications related to the procedure will be covered by insurance.

16) Economic Burden to Subjects

No economic burden to patients as TAP blocks are already planned for these patients' surgical operations. Exparel is FDA approved for this use. UCDMC formulary restricts Exparel use and requires IRB approval for this application. Within an IRB approved protocol the medication would be billed for as with all other medications given to the patient. There is no additional leave time planned for patients and these procedures will decrease the patients' postoperative pain control and may allow them to be discharged sooner.

17) Drugs or Devices

The study medication, liposomal bupivacaine (Exparel) will be obtained from the inpatient pharmacy prior to administration of the TAP block. All anesthesiologists performing the TAP block will have had prior education about the proper administration and dilution of the Exparel single shot injections. If the patient is receiving TAP block catheters, then the ropivicaine 0.25% medication is obtained from the acute pain block cart per protocol by the pain service.

18) ClinicalTrials.gov Registration

Section 1: NIH Funded Studies

If yes to BOTH, the study must be registered on Clinicaltrials.gov.

Yes	
☐	This study is funded by the NIH. (If this study is not funded by NIH, go to Section 2.)
☐	One or more human subjects will be prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

Section 2: Studies subject to FDA jurisdiction

If yes to ANY the study must be registered on Clinicaltrials.gov.

Yes	
☐	This is a prospective clinical study of health outcomes in human subjects that compares an intervention with an FDA-regulated device against a control. This is not a small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes.
☐	This is a pediatric postmarket surveillance of a device as required under section 522 of the Federal Food, Drug, and Cosmetic Act.
☐	This is a controlled clinical investigation, other than a phase I clinical investigation, of a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to section 351 of the Public Health Service Act.

To view a flowchart describing applicable clinical trials subject to FDA jurisdiction click here.

Section 3: Publishing the results

If yes to BOTH the study must be registered on Clinicaltrials.gov.

Yes	
☒	This study prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the cause-and-effect relationship between a health-related intervention *and* a health outcome.
☒	The PI has access to and control over all the data from the clinical trial and has the right to publish the results of the trial and plans to publish the results in a journal that follows the ICMJE recommendations.

This requirement includes studies of behavioral interventions.

Section 4: Registration on Clinicaltrials.gov is not required

Yes	
☐	I have read sections 1-3 above and registration on clinicaltrials.gov is not required for this research.