TRANSVERSUS ABDOMINIS PLANE (TAP) BLOCK STUDY FOR POSTOPERATIVE PAIN CONTROL

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Protocol Number: MZ2014035_TAP

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A Introduction

Study Abstract

As an anesthesiologist our goal is not only to ensure the patient does well during the operation but to also assist in the post-operative recovery period. Crucial to this is controlling post-op pain. A patient with poorly controlled pain will have trouble ambulating after surgery, taking deep breaths, and performing daily activities. This predisposes the patient to comorbidities including infectious processes such as developing pneumonia and impairs the healing response which requires adequate oxygen delivery to critical tissue beds. Furthermore, blocking perception of pain prevents development of chronic pain syndromes. Thus, blocking the response to pain plays a critical role in anesthesiology.

Furthermore, opioids are well known immune system suppressants. Regional analgesic techniques that limit the use of opioids for postoperative pain may lower the risk for metastasis and recurrence of certain cancers. The body's response to the stress of surgical trauma may also facilitate a release of tumor cells into the circulation [1-3] General anesthetic agents and opioids can suppress the immune response, and may further affect the functions of certain cells.[1,3] These immune inhibiting effects, combined with the immunosuppression related to acute pain may promote the evolution of cancer cells in clinical metastases by providing a conduit for tumors to proliferate.[1,3]

For many of our patients who undergo lower abdominal surgeries we choose a general anesthetic along with a regional technique called a TAP (transversus abdominis plane) block. The purpose of the latter is to treat the patient's post-operative pain. The name of this block is derived from relationship of the nerves that provide sensation to the abdomen and the muscle layers (namely the internal oblique and the transversus abdominis abdominal muscles) these nerves pass through. This is referred to as the TAP space. Although the TAP block has existed in anesthesia for decades it was not utilized much until the recent introduction of ultrasound imaging into anesthesia practice. Prior to the availability of ultrasound imaging, the TAP block was performed blindly and sometimes with inadequate pain relief. Now via an ultrasound probe we can clearly see the muscle layers and visualize the placement of the local anesthetic or catheter into the TAP space area. The goal of this block is to inject, usually under ultrasound guidance, a local anesthetic such as Bupivacaine in said space; thus, effectively blunting the patients perception of abdominal pain due to incision from surgery.[4-6] Depending on the amount of drug injected the block can last anywhere between 20-30 hrs, which correlates with the time period patients would report the most discomfort from incisional pain.

By placing a small catheter in the TAP space (continuous TAP block), local anesthetic can be continuously infused for a period of a few days thus extending the duration of pain relief up to 3 days.[7] Recently, the pharmaceutical drug Exparel has gained acceptance as a local anesthetic to be used for local infiltration of incisional sites including infiltrative blocks such as the TAP block. Exparel® combines the local anesthetic Bupivacaine with an injectable liposomal delivery system called DepoFoam. The pharmacokinetics of this delivery system is suggested to provide a continuous release of Bupivacaine over 3 days. Thus, it can be argued if a single

injection of Exparel can provide adequate pain relief over 3 days it can make obsolete the need to place a continuous nerve block catheter. There are significant benefits to this. It requires more skill and time to place a catheter versus a single injection of a local anesthetic for a TAP block. Other benefits are related to the avoidance of catheter maintenance including dressings, leakage at catheter insertion site, and the need for additional infusion pumps. Furthermore, any catheter has the possibility of infection or bleeding.

It is the purpose of this study to evaluate the efficacy of methods that allow for continuous release of local anesthetic in the TAP space, either via catheter or via injecting Exparel® a slow release liposomal space versus the standard single injection Bupivacaine in the TAP space. The study shall consist of three (3) arms of which patients will be randomly assigned: Continuous TAP block (CTAP) via Catheter, Single Injection TAP block with the slow release liposomal Exparel, and Single Injection TAP block with Bupivacaine. Several parameters will be measured with the primary goal being to determine the effectiveness and duration of post-operative pain relief.[8,9]

Primary Hypothesis

Methods that allow for continuous release of local anesthetic in the TAP space will decrease total narcotic requirements vs. the standard single shot Bupivacaine control. A continuous release of local anesthetic in the TAP space via catheters over 2 days will result in lower total narcotic requirements when compared to the single shot Bupivacaine injection technique when measured over 48 hrs. The Liposomal agent Exparel® which releases the Bupivacaine local anesthetic over three days should also allow for a single injection technique that can provide similar post-operative pain response to that of the catheter method without the need to place a catheter in the TAP space. Post-operative narcotic requirements are inversely related to post-operative pain control and patient satisfaction and total narcotic requirements will be significantly higher in the single shot group vs. the continuous release groups over 48 hrs.

Purpose of the Study Protocol

The purpose of this study protocol is to ensure consistent implementation of this study across all study sites.

B Background

Prior Literature and Studies

The analgesic efficacy of the TAP block has been demonstrated in prospective randomized trials compared with placebo, in several surgical procedures such as abdominal surgery[3], hysterectomy[2], retro-pubic prostatectomy[1], Caesarean section[7], laparoscopic cholecystectomy[5], and appendicectomy[6]. These studies reported superiority of the TAP block in terms of reduction in visual analogue scale scores and narcotic consumption. In two of the studies, the authors suggest the decrease in morphine consumption lasted for 2 days[4]. However, this difference was established during the first 24 hr. and remained stable thereafter. Therefore, we can assume the analgesic effect of the TAP block persists for at least 24 hr. and the TAP block should be

considered an integral part of a multimodal analgesic strategy including systemic analgesic agents to control residual pain. The fact that the TAP block may contribute to decreasing the incidence of narcotic side effects such as nausea and vomiting is also beneficial to the patient's rehabilitation.

Rao Kadam, et al., compared epidural to continuous TAP block, Epidural versus continuous transversus abdominis plane catheter technique for postoperative analgesia after abdominal surgery[10], finding no significant difference in terms of post-operative narcotic requirements. Although the study was underpowered, given the accepted and well-studied use of thoracic epidural for controlling post-operative pain, this is highly suggestive of the Continuous TAP block's efficacy for controlling post-operative pain.

Petersen, et al., demonstrated the spread of the TAP sensory block is also partly maintained by a continuous 24 hour Ropivacaine infusion via a TAP catheter versus a placebo *infusion, transversus abdominis plane (TAP) block with 24 hours Ropivacaine infusion via TAP catheters: A randomized trial in healthy volunteers*[7].

Xan Jacobs, et al., conducted a Retrospective Review of Exparel® in Infiltration-transversus Abdominis Plane (i-TAP) Blocks in Hand-assisted Nephrectomy and Colorectal Procedures[11]. These findings suggest that that the use of Exparel® in i-TAP blocks is a useful adjunct to postoperative pain control up to 72 hours post-injection in those patients undergoing hand-assisted abdominal procedures. This study also suggests a favorable safety profile with no adverse events related to the use of Exparel in an infiltrative TAP block.

Although, there is a fair amount of literature and case reports for TAP block for post-op pain; there is very little data that goes out as far as 72 hrs. Furthermore, those studies (albeit limited) demonstrate a difference that is not considered statistically significant between single shot TAP block and controls that did not receive TAP block at 72 hrs. Studies do however show a statistically significant difference in narcotic requirements and pain scores at 24 hrs (post-operative day [POD] #1), and at 48hrs (POD #2) between single shot TAP and placebo [4,12] and also between continuous TAP techniques and placebo[13]. However, no direct comparison study exists between continuous TAP Block techniques and standard single shot Bupivacaine technique. Using prior studies as a reference and making the appropriate equianalagesic conversions to account for the difference in narcotic potencies used in the various studies we can come to the expectation that total hydromorphone (Dilaudid) requirements would be roughly 50% lower in the continuous catheter TAP technique vs. the standard single shot Bupivacaine TAP technique at 48hrs. We estimate total Hydromorphone requirements over 48 hrs. in the control (single shot TAP) to be equal to 4.1mg versus the continuous catheter TAP group equaling 2.4 mg. We would also assume Exparel TAP to be equal to catheter TAP at 2.4 mg. Furthermore, Visual Analog Scales as expected follow a similar trend, with the most significant difference seen at 48 hrs.[4,11-13]

Rationale for this Study

The rationale for this study is to examine the post-operative pain benefits of continuous release TAP techniques (Catheter technique and liposomal slow release Exparel® technique) versus the

standard single shot Bupivacaine injection for TAP block. Therefore, in this study the standard single shot Bupivacaine technique acts as the control.

Although both modalities of continuous release TAP block have been proven versus placebo to provide post-operative pain relief over an extended time period; there is no such study that directly compares the standard single shot Bupivacaine technique to the continuous release TAP techniques in terms of quality or ability to control post-operative pain. Given the significant increased cost along with in the case of the catheter group skill, procedural time, and maintenance management there should be a significant improvement in post-operative pain duration versus the single shot Bupivacaine TAP block technique.

Furthermore, our expectation is that this difference will be most apparent at 48 hrs. as discussed above with a reduction in narcotic requirements greater than 40% in the continuous catheter TAP group vs. standard single shot Bupivacaine TAP (4.1 mg +/- 3 mg vs. 2.4 mg +/- 1.3 mg Dilaudid). This is based on the assumption that the effects of the local anesthetic control TAP (single shot Bupivacaine) may last up to 24 hrs. At 72 hrs, prior studies, although limited, have not shown a significant difference between TAP block and placebo groups.

C Study Objectives

Primary Aim

The primary aim is to evaluate for any significant difference total post-operative narcotic requirements (Dilaudid) required over 48 hrs. in the continuous catheter TAP block arm vs. the single shot Bupivacaine TAP arm and again the slow release Liposomal Exparel® TAP arm vs. the single shot Bupivacaine TAP arm.

Secondary Aim

The secondary aim will be to evaluate for any significant difference in narcotic requirements at other endpoints such as 24 hrs and at 72 hrs. As discussed before, current studies do not show a significant difference when extrapolated out at those end points, albeit there is very little data at 72 hrs. Other quality indicators of recovery in the three arms such as Visual Analog Scores (VAS) are expected again to be most significantly different at 48 hrs. Other quality measures that will be recorded include incidence and severity of post-operative nausea and vomiting (PONV), time to ambulation, and patient satisfaction with post-operative pain control.

Rationale for the Selection of Outcome Measures

Outcome measurements are based on the assumption that narcotic requirements (i.e. intravenous Dilaudid Patient-Controlled Analgesia [PCA] use) are inversely related to patient satisfaction in regards to their post-operative pain. Additional factors such as VAS, ambulation, performance of daily activities, and anti-emetic pharmaceutical requirements have been chosen as quality indicators in regards to post-operative pain control and dependence on narcotics.

D Investigational Agent

This investigation will use three FDA-approved techniques:

- Bilateral Continuous TAP block via Catheter (One-time bolus of Bupivacaine 0.25% x 20ml per side followed by continuous infusion of Ropivacaine 0.2% 7 ml/hr. per side x 48 hrs.);
- Single Injection TAP block with Exparel® (One-time bolus of Bupivacaine 0.25% x 20 ml followed by Exparel 133 mg per side); and
- Single Injection TAP block with Bupivacaine 0.25% (25 ml-30 ml volume one-time bolus per side).

E Study Design

Overview or Design Summary

It is the purpose of this study to evaluate the efficacy of continuous TAP block via catheter versus single shot Bupivacaine TAP block and also to evaluate the efficacy of slow release Exparel® versus single shot Bupivacaine The study shall consist of three (3) arms of which patients will be randomly assigned: Bilateral Continuous TAP block via Catheter (One time bolus of Bupivacaine 0.25% x 20 ml per side followed by continuous infusion of Ropivacaine 0.2% 7 ml/hr. per side x 48 hrs); Single Injection TAP block with Exparel® (One time bolus of Bupivacaine 0.25% x 20 ml followed by Exparel 133 mg per side); and Single Injection TAP block with Bupivacaine 0.25% (25-30 ml volume one time bolus per side). Several parameters will be measured with the primary goal being to determine the effectiveness and duration of post-operative pain relief of the newer techniques of extending TAP block duration with the current, commonly used standard single shot Bupivacaine technique. Because a goal of this study is to determine which technique of TAP block is most effective for post-operative pain control, the three (3) arms of this study will be performed in a manner that is most consistent and common with current anesthesia practice. Because TAP block is typically most effective for lower and mid-abdominal incisional pain relief, the nature and height of the incision with regard to the umbilicus will also be recorded.

Parameters Measured:

1) Total Post-operative Narcotic Requirements over at 24, 48 and 72hrs.

2) Days of IV PCA use: Time to 1st dose, total IV PCA requirements, POD# 0, 1, 2, & 3, additional narcotic use and additional adjuvants

3) PACU narcotic requirements

4) Pain Score:0-10 on post-operative day (POD)# 0, POD #1, POD #2, POD #3 (am, pm, Max Pain score per day, Pain score at rest, and Pain score with activity)

5) Day to Ambulation: O=out of bed assisted/unassisted, W= walk with/without assistance

6) Day of Foley removal

7) Day of first Bowel Movement

8) Anti-emetic Drug (Zofran) requirements.

9) Surgical Incisional height in relation to umbilicus or Type of Surgery (recorded by anesthesiologist)

10) Anesthesia provider placing TAP block

11) Patient weight/BMI

12) Day of discharge

Subject Selection and Withdrawal

Patients who would normally be selected to receive a TAP block, e.g., those patients with an abdominal or pelvic incision of the degree that would benefit from a TAP block, will be randomly assigned to one of three arms: TAP block via Catheter, TAP block via single shot injection of Bupivacaine, TAP block via single shot injection of Exparel. Patients may elect not to have a TAP block performed. Patients with indwelling TAP block catheters may at any time elect to have their TAP block catheters removed prior to the completion of 72 hrs. of treatment.

E2.a Inclusion Criteria

i Participants will have signed a informed consent.

ii Participants will be 18 years or older

iii Scheduled for open abdominal surgery

iv American Society of Anesthesiologists physical status (ASA) 1-3

E2.b Exclusion Criteria

i Participants are not able to understand or provide written informed consent, or for children, are unable to assent.

ii The research team deems that the participant may not be able to follow the study protocol.

iii Complicated history of chronic opioid use

iv Allergy to local anesthetics

v Contraindication to regional nerve block (bleeding disorder, sepsis or infection at site)

vi BMI >40 because of difficulty in placing the catheter

vii Pregnancy

viii Complicated history of chronic opioid use including the daily use of opioids for a period of greater than 2 weeks prior to surgery

E2.c Ethical Considerations

This study will be conducted following all local laws and regulations in the conduct of research, as well as the International Conference on Harmonisation Good Clinical Practice Guidelines. These guidelines provide a unified standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects.

In addition, this study will be reviewed and approved by appropriate Institutional Review Boards prior to the initiation of any study procedures. Any modifications to this protocol will be submitted to and approved prior to submission to the appropriate Institutional Review Board(s) prior to initiation unless implementation is required to avoid an apparent immediate hazard for subjects. The protocol will undergo continuing review and approval by all IRB's providing ongoing oversight of the study.

E2.d Subject Recruitment Plans and Consent Process

Subjects will be consented using a current informed consent form that has been approved by the respective study site's Institutional Review Board. Subjects will be allowed adequate time to read the informed consent, discuss the consent with study staff and others (e.g., family members, friends, or any of their health care providers), and have their questions answered prior to signing the informed consent. In some cases, a site may not accrue study subjects but serve as a data analysis site so informed consent may be waived for that site.

Site-specific recruitment plans and consent process are outlined in Attachment L1.

E2.e Randomization Method and Blinding

Subjects that would normally be selected to receive a TAP block will be randomly assigned into one of the three arms. A random number generator will be used to generate an equal proportion of responses of the three arms. These responses will be sealed in envelope. The anesthesia provider will be allowed to open the envelope and become aware of the selected arm after the initiation of anesthesia (this would include the administration of a pre-medication or initiation of general anesthesia). Complete blinding is impossible to staff given the visual presence of a catheter in some groups versus the lack of catheters in other groups. In addition, the agent Exparel® has a milky color that is obvious to the anesthesia provider injecting it. However, the nursing staff on the floor will not be made aware of the use of Exparel® versus Bupivacaine in the single injection arms.

E2.f Risks and Benefits

i Risks

Potential physical risks include:

TAP block is a relatively low risk regional anesthesia technique with a long track record. However, any injection or insertion of a catheter into the body carries a slight risk of bleeding, bruising at injection or insertion site, and infection at injection or insertion site. Risks particular to an injection of a local anesthetic into the abdominal area would be bowel perforation, local anesthetic toxicity, and drug allergy. These risks are unlikely and similar to an abdominal paracentesis. Furthermore, the author is unaware of any episodes of bowel perforation from the administration of a TAP block.

The following are side effects have been seen with the local anesthetics Bupivacaine and Ropivacaine:

- Low blood pressure
- Nausea and/or vomiting
- Slow heartbeat
- Fever
- Pain
- Post-operative complications
- Low blood hemoglobin (anemia)
- Tingling of the fingers or toes
- Headache
- Itching
- Back pain
- Retention of urine or low urine output
- Dizziness
- Decreased touch sensation
- Anxiety
- Chest pain
- Low blood potassium
- Shortness of breath
- Muscle cramps
- Urinary tract infection

The following are side effects have been seen with Exparel®

- Nausea
- Constipation
- Vomiting
- Fever
- Dizziness
- Swelling of the arms or legs
- Anemia (including post-operative or due to bleeding)
- Low blood pressure
- Itching
- Rapid heartbeat
- Headache
- Insomnia
- Muscle spasms
- Back pain
- Sleepiness
- Procedure pain

Potential psychological risks include:

Catheter leakage at insertion site may cause dissatisfaction in that specific study arm. Also leakage may cause perceived risk of catheter dysfunction to the patient. Because leakage can occur in a fully functioning catheter this may influence patients reported post-op pain response. Also, due to the slightly increased risk of infection in the catheter group, any signs of infection would cause significant dissatisfaction in that specific arm. In addition, the visual sight of catheters along with a pump may cause the patient anxiety along the feeling of additional tubes preventing daily activity. This will be minimized by

maintaining a clean dressing over the catheter site and the use of a fanny pack the patient wears at their waist side that will contain the OnQ® infusion system.

Potential social risks include:

There is a possible social risk of embarrassment or reputational standing while responding to questionnaires or interviews.

Using trained interviewers and maintaining your records in locked cabinets or secure computer files will minimize this risk.

ii Benefits

The benefits that the subject may get from being in this study are improved post-operative pain response and quicker recovery time following surgery. A patient with improved post-operative pain will be at lower risk for pulmonary infection and circulatory issues because they will ambulate sooner along with decreased degree of pulmonary atelectasis. Decreased dependence on narcotics will also lead to faster recovery of bowel function. This overall will lead to increased patient satisfaction and earlier discharge from the hospital.

Early Withdrawal of Subjects

Subjects may be withdrawn for the following reasons:

Subjects may be withdrawn from the study early due to complications secondary to the surgery itself such as sepsis, bowel dysfunction unrelated to narcotic use, and the need for further exploratory surgery.

Catheter dysfunction due to dislodgment or severe leakage may also precipitate early withdrawal from the study. Bleeding, infection, or need to anti-coagulate may cause premature need to remove the catheters from the patients. In these cases, the data will continue to be recorded as in the other arms; however, time of catheter removal will also be recorded.

Failure to perform an adequate block will also cause withdrawal from the study. Reasons for said failure would include: inability to visualize TAP space on ultrasound and surgical site preventing use of bilateral TAP block.

Failure to place catheter after successful bolus of local anesthetic would move patients from the CTAP group to an un-randomized single shot Bupivacaine arm. Patients will be followed until completion of the study. This data may be analyzed separate or as part of the single shot Bupivacaine group.

Failed block is a withdrawal prior to first study follow up; these patients would need to be replaced or moved to an open un-randomized arm.

Subjects may also be withdrawn from the study if it at any time it is determined that they did not meet inclusion exclusion criteria.

iii Subject safety

iv Non-compliance with study visit schedule or study regimen

Subjects may be involuntarily exited from the study for failure to comply with the protocol, failure to attend follow-up visits, or for other reasons. The investigator shall arrange for an exit visit and complete the case report form for the subject to the extent there is data available.

Subjects may voluntarily withdraw from the study at any time without reason. The investigator shall make an effort to obtain an exit visit and complete the case report form for the subject to the extent there is data available. The investigator cannot require that an exit interview take place.

E2.g Data Collection and Follow-up for Withdrawn Subjects

1) Reason for withdrawal from study (i.e. block failure, catheter failure, drug toxicity, sepsis, patient request)
2) Day of withdrawal from study

Study Drug/Device

E3.a Description

The ON-Q® device is considered a non-significant risk device which has been marketed for postoperative pain management since 1998.

Description of Device:

The ON-Q® Pain Management System (Device), an FDA-cleared disposable elastomeric infusion pump designed to deliver local anesthetic to or near the surgical sites or nerve bundles to relieve postoperative pain.

A capillary flow-restricting orifice located at the end of the tubing and the positive pressure system of the elastomeric infusion pump maintains a consistent flow rate.

The pump is filled in a sterile fashion in either pharmacy or the operating room with local anesthetic, and connected to a Catheter, which is placed by the anesthesiologist or the surgeon, in a sterile fashion, tunneled to an appropriate location. The pump offers a continuous regulated infusion at a rate determined by the anesthesiologist or surgeon. It is small, completely portable, and can be attached to the patient's gown or worn in a small wait pack to facilitate ambulation. The device used for the Study will be a standard unit of the device as produced for sale, with no modifications to the device or changes to the labeling.

Description of Drugs use for other two arms:

Exparel: Exparel is an extended release liposome injection of bupivacaine designed to achieve long-acting postoperative analgesia. The drug consists of microscopic,

spherical, lipid-based particles (the DepoFoam drug delivery system) composed of a honeycomb of numerous, nonconcentric, internal aqueous chambers containing the encapsulated bupivacaine. Each chamber is separated from adjacent chambers by lipid membranes. This product was originally named Skye and then following transition of ownership of the product by Pacira was termed generically as DepoFoam® bupivacaine.

Ropivacaine Naropin™: Ropivacaine Hydrochloride is a local anesthetic (injectable) of similar efficacy to Bupivacaine for use in surgery, postoperative pain management, and obstetrical procedures when local or regional anesthesia is needed. It can be administered via local infiltration, epidural block and epidural infusion, or intermittent bolus. Although similar to the local anesthetic Bupivacaine, it does have a more favorable cardiac toxicity profile when given in large doses.

Description of standardized protocol for the treatment of breakthrough pain including all adjunctive therapies given for pain management:

Initial rescue IV pain medication will be made available similarly in all three study arms and will consist primarily of the IV opioids Dilaudid (or Morphine if patient does not tolerate Dilaudid).

All post-surgical patients are given a Dilaudid (or the equivalent dose of Morphine if not tolerated) IV PCA with every 10 minutes bolus function following surgery to be initiated immediately upon admission and transfer from the PACU to the floor. A clinician bolus of Dilaudid 0.5 mg every 30 minutes will be made available for additional pain control if needed.

Acetaminophen (Tylenol) will also be made available for treatment of post-operative pain on the floor.

Treatment Regimen

Patients assigned to the study group will randomly be assigned to one of the three arms described above. Patients in the catheter arm will receive a commercially available ON-Q® pain management system filled with 0.2% Ropivacaine. The ON-Q® system consists of an ON-Q® elastomeric infusion pump that will be connected to an end-orifice catheter. Patients in the catheter arm will receive a 20 ml bolus of Bupivacaine via Tuohy needle in the TAP space followed immediately by tunneling of a catheter into the TAP space under ultrasound guidanceprior to extubation and complete emergence from general anesthesia. Said catheter will be left to infuse continuous local anesthetic site up to post-operative day 3. Patients in the two (2) single injection arms will similarly receive a bilateral injection of study local anesthetic (Exparel or Bupivacaine) 25-30ml per side in the TAP space prior to the conclusion of surgery under ultrasound guidance. Intra-operatively patients in all three study arms will receive IV fentanyl and IV Acetaminophen 1000mg unless drug allergy or intolerance to either medication.

Initial rescue IV pain medication will be made available similarly in all three study arms according to the institution's protocol for PACU breakthrough pain and will consist primarily of IV Dilaudid (or Morphine equivalent if patient does not tolerate Dilaudid). All post-surgical patients are given a Dilaudid (or Morphine if not tolerated) IV PCA with q10min bolus function following surgery to be initiated immediately upon admission and transfer from the PACU to the floor. A clinician bolus of Dilaudid 0.5 mg every 30 minutes (or Morphine equivalent) will be made available for additional pain control if needed. Tylenol will also be made available for treatment of post-operative pain on the floor.

E3.b Method for Assigning Subjects to Treatment Groups

Randomization will occur following the consent process and prior to surgery. The on-site personnel will manage the randomization. A random number generator will be used to assign patients to one of three arms and the anesthesia provider will be unaware of which arm the patient is assigned to until after initiation of anesthesia (see section E2.e).

E3.c Preparation and Administration of Study Drug

Patients in the single shot arms (Bupivacaine 0.25% and Exparel) will receive bilateral bolus injections of the local anesthetic t prior to extubation (waking up from General Anesthesia). Patients in the continuous catheter arm will also receive a bolus injection of local anesthetic prior to the placement of the catheter. Those patients will also receive a pump.

1) Bupivacaine 0.25% Arm: A total of 60 ml Bupivacaine 0.25% from two 30 ml vials will be pre-drawn up via 60 ml Syringe. The syringe will be connected and a 10ml flush syringe containing 10ml 0.9 NS will be connected to the end of an IV extension set via a 3-way stopcock and luer lock connections. The Bupivacaine 0.25% syringe will also be connected to the stopcock. The distal end of the IV connection will be maintained sterile and will be connected to the injection needle. Then the procedure is as follows: Step 1) The entire setup will be flushed with 0.9NS via flush syringe. 2) The TAP space will be located under ultrasound guidance and verified by using the 0.9% NS flush syringe. Once in the TAP space, 30 ml Bupivacaine 0.25% will be injected into the TAP space (This dose will be decreased to 25ml for patients under 70 kg). Steps 2 and 3 will be repeated on the opposite side TAP block.

2) Exparel Arm: The entire contents of one 20 ml Exparel vial (266 mg) will be drawn up 20 ml syringe. 40ml Bupivacaine 0.25% will be pre-drawn into 2x 20 ml syringes and connected to a stopcock. The syringe containing the Exparel solution will also be connected to the stopcock. The distal end of the IV connection will be maintained sterile and will be connected to the injection needle. Procedure Step: 1) The entire setup

will be flushed with the Bupivacaine syringe. 2) The TAP space will be located using the Bupivacaine syringe under ultrasound guidance. 3) Once the TAP space, Exparel 133mg will be injected into the TAP space. 4.) After injection, the syringe will be exchanged for the Bupivacaine syringe and the residual Bupivacaine will be injected into the space (~20ml). Steps 2-4 will be repeated for the opposite side TAP block.

3) Continuous Catheter Arm: A total of 40 ml Bupivacaine 0.25% vials will be pre-drawn up via two 20 ml Syringes. The Bupivacaine 20ml syringe will be connected to IV tubing. The distal end of the IV connection will be maintained sterile and will be connected to the injection touhy needle. Procedure step 1) The entire setup will be flushed with the Bupivacaine syringe. 2) The TAP space will be located using the Bupivacaine syringe and ultrasound guidance. 3) Once in the TAP space, 5-10ml Bupivacaine 0.25% will be injected into the TAP space. The IV extension will then be disconnected from the touhy needle and a catheter will then be threaded via the touhy needle and into the TAP space. The proximal end of the catheter will then be connected to the distal end of the IV extension set and the residual Bupivacaine 0.25% from the 20ml syringe will then be injected thru the catheter. The catheter will then be secured and dressed via standard technique for catheter placement. Steps 2-4 will then be repeated for the opposite side TAP block. In the PACU, patients will receive a pre-filled ON-Q® system obtained through the hospital pharmaceutical department. The pre-filled ON-Q® system contains Ropivacaine 0.2% in a 700 ml container. The infusion pump will be set to run at a rate of 7 ml/hr. per side.

Breakthrough pain will be managed similarly in all three arms via Dilaudid IV PCA every 10 minutes with clinician bolus function of 0.5 mg every 30 minutes.

E3.d Subject Compliance Monitoring

The Principal Investigator will oversee compliance with study procedures.

E3.e Prior and Concomitant Therapy

N/A

E3.f Packaging/Labeling

N/A

E3.g Blinding of Study Drug

It will be impossible to blind the catheter group from practitioners and floor care nurses given the obvious appearance of the catheters. However, the floor care nursing and staff will be blinded between the single injection arms: Exparel and Ropivacaine. The

anesthesia provider placing the block will similarly not be blinded given the need to place the catheters and the milky coloration of the Exparel drug when compared to Bupivacaine.

E3.h Receiving, Storage, Dispensing and Return

Study medications will be dispensed from the pharmacy according to usual procedures.

F Study Procedures

Screening for Eligibility

We will review the patient's medical records to determine study eligibility prior to obtaining consent of the patient to participate in the study. No research-specific information will be collected prior to the informed consent process.

The site-specific screening procedures are outlined in Attachment L1.

Schedule of Measurements

See Attachment L2 for a Table of the Schedule of Measurements/Calendar.

Safety and Adverse Events

F3.a Safety and Compliance Monitoring

The lead study investigator will monitor the safety and compliance of all study sites utilizing the Oncore ERM study management system.

F3.b Medical Monitoring

i Investigator only

This study is a comparison of three usual care regimens for the prevention and treatment of post-operative pain. The Investigator will be responsible for all medical monitoring through the course of providing usual patient care.

ii Independent expert to monitor

The Human Research Protection Program of Medicine and Science monitors all investigator-initiated research. Reports of monitoring visits are provided to the Principal Investigator and the Director of HRPP.

iii Institutional Data and Safety Monitoring Board

The Institutional Review Board will provide safety oversight for this study.

iv Independent Data and Safety Monitoring Board

No Independent Data and Safety Monitoring Board will be created for this study.

F3.c Definitions of Adverse Events

Adverse events will comprise all events that are untoward changes from a subject's baseline condition.

3.d Classification of Events

i Relationship

The investigator will determine the relationship of an adverse event to the TAP Block procedure.

ii Severity

The Investigator will assess the severity of adverse events in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

iii Expectedness

Adverse events listed in the protocol, IRB-approved informed consent form, or drug specific, FDA-approved package inserts will be considered to be foreseeable risks of participation in the study. Other adverse events will be considered unexpected.

F3.d Data Collection Procedures for Adverse Events

Please see Attachment L2 for data collection form. All adverse event data will be entered into Oncore ERM.

F3.e Reporting Procedures

Serious Adverse Events and adverse events that meet "severe" criteria must be directly reported within 24 hours to the Principal Investigator, and the IRB.

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Department of Anesthesiology
Midwestern Regional Medical Center
Zion, IL

Other adverse events must be entered within 7 days of collection into the Oncore ERM.

F3.f Post-study Adverse Event

Serious Adverse Events and adverse events that meet "severe" criteria must be directly reported within 24 hours to, the Principal Investigator and the IRB.

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Other adverse events must be entered within 7 days of collection into the Oncore ERM.

F3 Study Outcome Measurements and Ascertainment

G Statistical Plan

Interim Monitoring and Early Stopping

The Principal Investigator will utilize the Oncore ERM study management system to monitor the study.

The study may be stopped early for the following reasons:

- withdrawal of funding
- safety issues
- drug has been proven effective and no further testing is needed

Analysis Plan

The study is a prospective, randomized, open, active controlled clinical trial. Effectiveness of the Continuous TAP (CTAP) via the ON-Q® Pain Management System will be evaluated and compared to single shot techniques with respect to reductions in postoperative opioid consumption over the first 72 hours postoperatively. Secondary outcomes including hospital length of stay (LOS), time in PACU, pain at rest and with activity, return of bowel function, and incidence of opioid related side effects will also be evaluated.

The aims of this study are to compare the efficacy of continuous TAP block via ON-Q® system versus that of single injection techniques for TAP block regarding opioid reduction among patients undergoing major abdominal surgery. It is hypothesized that a continuous TAP block technique reduces pain, the need for opioids as well as the expected length of stay relative to those resulting from those subjects receiving a single TAP injection of Exparel (liposomal Bupivacaine) or single TAP injection of Ropivacaine to treat postoperative pain.

Study success criteria:

Based on the above hypothesis this study will be considered successful in demonstrating superior efficacy relative to control if consumption of opioids postoperative is significantly less among patients randomized to receive a

continuous TAP block via the ON-Q® system compared to the patients randomized to receive a single TAP injection of Exparel (liposomal bupivacaine) or single TAP injection of Ropivacaine to treat postoperative pain. However, a finding of no difference between the continuous catheter technique and the Exparel arm would also be considered beneficial to the advancement of post-operative pain control techniques because it would demonstrate similar post-operative pain control can be achieved without the extra time and skill required to place a catheter.

Statistical Methods

Sample Size

The main objective of study is to compare total opioid consumption between the single shot TAP group and the Exparel TAP group with a parallel design. Based on previous studies and internal pilots, the mean total opioid consumption (standard deviation) was 4.1 mg (SD 3 mg) in single shot group and 2.4 mg (SD 1.3 mg) in Exparel TAP group. For the sample size calculation, a standard deviation of 3 is used as a conservative estimate. To detect a difference in mean opioid consumption between treatment groups, 4.1 mg vs. 2.4 mg, a sample size of 49 patients per arm is required to achieve 80% power with a significance level of 0.05 using a two-sided t-test or Wilcoxon rank-sum test depending on normality test. A secondary aim is to examine a difference in mean opioid consumption between the single shot TAP group and continuous TAP group. Allowing for a 10% dropout rate, a total of 159 participants with 53 participants in each arm will therefore need to be recruited into the study. It anticipated that approximately 8 participants per week will be enrolled into this study, thus the estimated accrual time is around 1 year.

Statistical Analysis Plan

All analyses will be conducted on patients following an intention-to-treat principle, including all randomized participants enrolled in three arms, in case of relevant non-compliance to the treatment and/or impossibility to evaluate the endpoints, a per-protocol analysis will also be performed, together with an analysis of non-compliance/non-evaluation.

Patient characteristics and outcomes data will be summarized by cross-tabulation (categorical variables), quartiles (median, ordinal variables), and mean and standard deviation (continuous variables). Comparisons between groups will use Chi-square test or Fisher's exact test as appropriate for categorical variables and t-test or Wilcoxon rank-sum test as appropriate for continuous variables.

Analyses of primary outcome will examine differences in mean opioid consumption between the single shot TAP group and the Exparel TAP group. Analyses of secondary outcomes will examine differences in mean opioid consumption between the single shot TAP group and continuous TAP group. Treatment groups will be compared using a

student's t-test if data are normal distributed or Wilcoxon rank-sum test if not normal distributed.

The differences in mean opioid consumption across three groups (single shot TAP, continuous TAP, and Exparel TAP) will be examined with a test of means between groups using one-way analysis of variance (ANOVA). A comparison between continuous TAP and Exparel TAP will be performed. A t-test will be used if the observations in each trial arm are normally distributed; if non-normally distributed, then rank-based methods such as Wilcoxon rank-sum test will be employed.

All tests will be two-sided.

The overall incidence of serious adverse events and adverse events and number and proportion of patients reporting such events will be summarized by treatment group. Adverse events will be tabulated and summarized by the number and percentage of subjects who experienced the event.

Missing Outcome Data

Analysis will be conducted as described in prior section. Missing data will not be included in the analysis; however, may lead to an increase in patients recruited into one or more study arms.

Unblinding Procedures

This study is not blinded because it will be obvious to all care givers whether or not the patient received a continuous block with catheters or not.

H Data Handling and Record Keeping

Confidentiality and Security

Data will be collected on the data collection forms located in Attachment L9 and entered into the Oncore ERM study management system.

Data collection forms will be stored at each respective study site within a locked cabinet in a locked research office.

The Oncore ERM study management system is a secure web-based management system that is password-protected. Access to data is role-specific.

All study sites will observe Health Insurance Portability and Accountability Act (HIPAA) Privacy and Security Rule standards.

Training

All research team members must complete approved Human Subjects and HIPAA training.

All research team members must complete Oncore ERM training.

Case Report Forms and Source Documents

Study sites will utilize the data collection forms in Attachment L9 to collect data and will enter data into the Oncore ERM study management system.

Records Retention

Paper study records will be maintained at the respective study sites for seven years from the end date of the study. At the end of this time period, study records will be shredded.

Data in the Oncore ERM study management system will be stored for seven years from the end date of the study. At the end of this time period, records will be deleted.

Performance Monitoring

The IRB and the Principal Investigator will monitor study performance using the Oncore ERM study management system.

I Study Monitoring, Auditing, and Inspecting

Study Monitoring Plan

The IRB and the Principal Investigator will monitor ongoing study performance using the Oncore ERM study management system.

Auditing and Inspecting

The IRB will audit and inspect study materials at the study sites as indicated.

J Study Administration

Organization and Participating Centers

The Principal Investigator at the lead institution will collaborate with study site Principal Investigators to oversee this study.

Funding Source and Conflicts of Interest

There are no conflicts of interest among any of the study investigators.

Study investigators must complete institution-specific conflict of interest forms as required.

Subject Stipends or Payments

Subjects will not be paid for their participation in the study.

Study Timetable

The study will last for approximately four months. This is the estimated time based on current operating room patient criteria to enroll ninety patients into the study.

K Publication Plan

Upon completion of study and statistical methods, it would be expected to publish the study in an established and well-read peer journal of either Anesthesiology or Surgery. Given that an analysis demonstrating a statistically significant difference or no difference between any of the study arms would be useful to how anesthesiologist and/or the surgical team approach the TAP block, it is highly likely the study would be accepted for publication.

L Attachments – TAP Block Pain Management Data Form

Schedule of Measurements Template (add addition information as needed)

Anesthesiologist performing TAP BLOCK	Surgeon
Date of Surgery	Hospital Discharge Date

Procedure ☐ Ventral hernia ☐ Expl. Lap ☐ Colon ☐ Small Bowel ☐ Anterior Resection ☐ APR ☐ Lower Anterior Resection ☐ Prostate ☐ TAH ☐ HIPEC ☐Cyto-reductive Surgery ☐ Ileostomy reversal ☐ Robotic Assisted +/- Hand Assisted ☐Robitic (no incision) ☐L/S Assisted +/- Hand Assisted ☐L/S (no incision) ☐ Other_____	☐ Continuous TAP with Ropiv 0.2% ☐ Single Shot TAP ☐ Exparel ☐ 0.25% Bupivicaine ☐ Pre-incision ☐ Post-incision Other:_____

PATIENT INFORMATION

Initials	**Outpatient / SDA** ☐ Patient taking narcotics at home prior to surgery? ☐Yes ☐ No	**Inpatient** (prior to Surgery) ☐ PCA ☐ IV narcotics ☐ (skip if PCA) P.O. Narcotics ☐ (skip if PCA)

Age	Gender ☐M ☐ F	Race ☐Cauc ☐Black (Non Hisp) ☐ Hisp ☐ Asian ☐ Other	ASA

BMI	Smoking ☐Yes ☐ No	Diabetes ☐Yes ☐ No	

Incisional Dermatone Level Range: (Umb=T10)	Surgery Duration (minutes)	PACU Time until nurse gives report

Outcomes **PCA**	PACU	POD 0 ☐ Y ☐ N	POD 1 ☐ Y ☐ N	POD 2 ☐ Y ☐ N	POD 3 ☐ Y ☐ N
NARCOTICS					
MSO4 (mg) total requirements					
Dilaudid (mg) total requirements					
Fentanyl (mg) total requirements					
Anti-emetic Given (+/-)					
EVENTS					
Bowel Movement (+/-) (record 1st day only)					
Urinary Catheter (+/-) (record up to removal					

only)					
Diet NPO, L=liquid FL=full liquid, N=Normal					
Pain (0-10) am At Rest / With Activity					
Pain (0-10) pm At Rest / With Activity					
Ambulation O= out of bed assisted W=Able to walk unassisted					

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