Comparison of Liposomal Bupivacaine, Plain Bupivacaine, and Placebo for Transversus Abdominis Plane Blocks:

A Randomized, Blinded Trial

NCT04685876

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Amendments

Amendment 1: 10/1/2021

Summary of Changes:

1. The primary outcome was changed to opioid consumption in the first 24 hours and 24-48 hours after surgery.
2. The secondary outcomes are now abdominal wall sensation with ice and pinprick, pain scores 72 hours after surgery, and opioid consumption 48-72 hours after surgery.
3. Sample Size Considerations was updated to reflect the changes in the study outcomes.

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Specific Aims

Pain management after major abdominal surgery remains challenging. The best-accepted traditional analgesic approach is continuous epidural analgesia. However, epidural analgesia is rapidly being replaced by transversus abdominis plane (TAP) blocks. TAP infiltration is an alternative to epidural blocks for providing postoperative analgesia to the anterior abdominal wall. TAP infiltrations are relatively easy to perform, generally safe, and can be performed in patients who are anti-coagulated. TAP infiltration can be performed as a single injection, or a catheter can be inserted for continuous local anesthetic infusion.

Single shot plain bupivacaine is often used for TAP blocks, but plain bupivacaine provides <24 hours of analgesia Catheters provide analgesia for longer, but they are difficult to position properly and difficult to maintain in the proper anatomical location. An alternative to TAP catheters is infiltration of liposomal bupivacaine which, in other sites, lasts up to three days. But whether liposomal bupivacaine is preferable to plain bupivacaine for TAP blocks remains controversial, with available studies being sparse and inconclusive.

We therefore proposed to compare single-shot TAP infiltration with liposomal bupivacaine, plain bupivacaine, and placebo on length of anesthetic effect determined by the opioid consumption. We will evaluate the following specific aims, all of which will be assessed over 72 hours, or the duration of hospitalization if shorter:

Primary Aim 1: To assess the relative effects of TAP blocks with liposomal bupivacaine, plain bupivacaine and placebo on cumulative opioid consumption in first 24 hours with TAP blocks.

Primary Aim 2: To assess the relative effects of TAP blocks with liposomal bupivacaine, plain bupivacaine and placebo on cumulative opioid consumption in 24 to 48 hours with TAP blocks.

Secondary Aim 1: To assess the relative effects of TAP blocks with liposomal bupivacaine, plain bupivacaine and placebo on the duration of abdominal wall analgesia (determined by pinprick and cold).

Secondary Aim 2: To assess the relative effects of TAP blocks with liposomal bupivacaine, plain bupivacaine and placebo on pain after surgery in first 72 hours.

Secondary Aim 3: To assess the relative effects of TAP blocks with liposomal bupivacaine, plain bupivacaine and placebo on cumulative opioid consumption 48 to 72 hours.

***Tertiary* Aim 1**: To compare the effects of TAP blocks with liposomal bupivacaine, plain bupivacaine, and placebo on a composite of postoperative opioid-related side effects.

***Tertiary* Aim 2:** To compare the effects of TAP blocks with liposomal bupivacaine, plain bupivacaine and placebo on patients' satisfaction with their pain treatments after 72 hours/discharge surgery.

Tertiary Aim 3: To assess total and specific costs of hospital care in patients receiving TAP with liposomal bupivacaine vs. those with plain bupivacaine following abdominal surgery. [2 groups only]

Tertiary Aim 4: To compare the effects of TAP blocks with liposomal bupivacaine, plain bupivacaine and placebo on patients' pain with movement for 72 hours/discharge surgery.

Tertiary Aim 5. To compare the effects of TAP blocks with liposomal bupivacaine, plain bupivacaine and placebo on patients' mobility for 72 hours/discharge surgery.

1. Background

A. Postoperative Pain

Pain is a psychological sensory experience that is provoked by surgical tissue injury. Postoperative pain results from a of combination of nociceptive and inflammatory components.[1] The nociceptive component results from activation of peripheral sensory neurons damaged by surgical incision and fades gradually as tissues heal. The inflammatory component enhances pain sensitivity via release of mediators from surgically injured tissue. Central neuronal sensitization also seems to contribute to postoperative pain and hyperalgesia.[1,2] Both mechanisms contribute to resting pain is in and around surgical incisions. Movement of wounds or touching them, breathing, coughing, and gastrointestinal motility can all provoke pain.

Postoperative pain causes a number physiological and psychological consequence, which potentially worsen outcomes. For example, inadequate perioperative analgesia is associated with myocardial ischemia, impaired wound healing, delayed gastrointestinal motility, atelectasis, and postoperative pneumonia.[3-5] Furthermore, poorly controlled acute pain is strongly associated with development of persistent incisional pain, which can be devastating for patients.[6,7]

B. Postoperative pain management and Regional Analgesia

Pain management after major abdominal surgery is difficult and complicated. Thirty percent of patients report severe postoperative pain and 47% report moderate pain.[8] Furthermore, 10-40% report persistent pain after abdominal and pelvic surgery.[9] Multimodal analgesia combines various classes of drugs in an effort to provide good analgesia with few side effects.[1,10,11] But the most common approaches are a combination of an opioid and non-opioid, with or without regional anesthesia-analgesia.[11] Opioids cause various complications including ileus, sedation, and hyperalgesia. Opioids also impair cellular and humoral immune function in humans, thereby potentially enhancing infection risk.[13-16] But the most lethal complication of opioid use is respiratory depression which has been identified as a safety target by the Joint Commission on Hospital Accreditation.[12] Reducing perioperative opioid use is thus a clinical priority.

Regional Anesthesia or analgesia reduces the need for high-dose opioids. Regional analgesia techniques can be categorized as neuraxial (spinal and epidural blocks) that involve injection of local anesthetics around the spinal cord, or as peripheral nerve blocks that involve local anesthetic administration near peripheral nerves. The basis of regional analgesia is local anesthetics which locally block voltage-gated sodium channels, thus interrupting nerve conductions and causing regions to be insensitive to pain.[17] Peripheral nerve blocks, especially, have become popular in recent decades largely because improvements in ultrasound technology make blocks faster and safer — and more importantly, because peripheral nerve blocks speed recovery and improve patient satisfaction.[18]

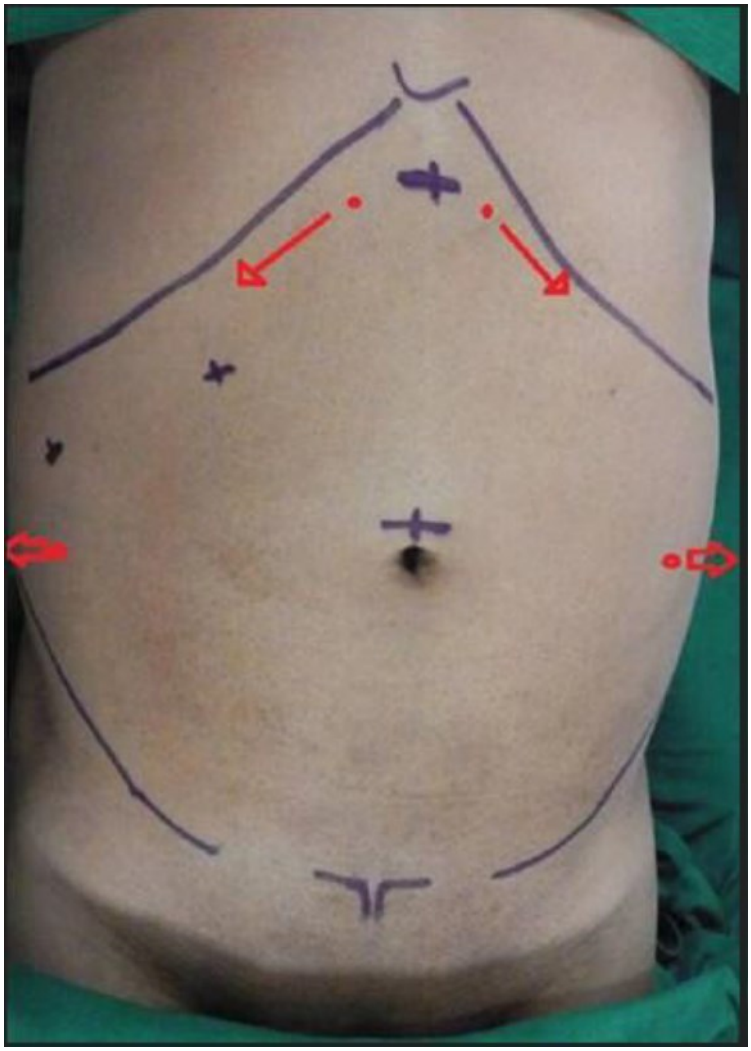
Surgery provokes a stress response which releases catecholamines, cortisol, and inflammatory cytokines systemically.[19] The stress response is associated with increased catabolism, immunosuppression, poor postoperative outcomes, and prolonged recovery.[20,21] Regional anesthesia blocks afferent neural transmission from reaching the central nervous system and activating the stress response, thereby blocking descending efferent activation of the sympathetic nervous system.[22-24] In clinical practice, regional anesthesia has proven to be superior to systemic opioids alone after thoracic, abdominal, gynecological, and orthopedic surgeries.[25-28] Studies have consistently shown that regional anesthesia reduces postoperative pulmonary, gastrointestinal, and cardiac morbidities. Furthermore, there is evidence that RA decreases postoperative morbidity and mortality, and shortens postoperative hospitalization.[29-32]

Epidural analgesia is the reference method for controlling post-operative pain after abdominal surgery. However epidural analgesia provokes hypotension, delays mobilization and discharge. Furthermore, catheter related problems are common, as is failure of epidural analgesia. Rarely, epidural analgesia results in inadvertent dural puncture, epidural hematoma, abscess, cord compression, and permanent paraplegia due to hematoma. An important limitation of epidural analgesia is that it should not be used in anticoagulated patients. These limitations have prompted clinicians to use alternative blocks, including the transvers abdominal block.

C. Transversus Abdominis Block

Transversus Abdominis Block was described by Rafi in 2001 and provides post-operative analgesia for anterior abdominal wall.[33] The target area of the local anesthetics is between the transvers abdominis and internal oblique muscle to block the spinal nerves (T6-L1). There are various types of TAP blocks, including intercostal/subcostal, lateral/classical, anterior, and posterior approaches.[34]

Figure 1: 4-quadrant TAP block



Ultrasound-guided TAP blocks are easier and safer than epidural blocks, and complications are rare. TAP blocks are generally performed with a single injection, because catheters are tricky to insert properly and are frequently dislodged, especially when they are near the surgical site.[44] TAP blocks have been used for various types of

surgeries including open appendectomies, hysterectomies, caesarean deliveries, abdominoplasties, prostatectomies, renal transplantation, and laparoscopic procedures.[35-41] In open gynecologic surgeries, cesarean deliveries, and open gastrectomies, bilateral TAP blocks provides better analgesia than placebo groups.[33]

All anterior branches of spinal nerves communicates, each segmental nerve supplies different areas and therefore analgesic effect and sensorial distribution of local anesthetics vary.[42] Four-quadrant TAP blocks (Bilateral Dual) were described by Borglum et al. and provides wider coverage for upper- and lower-abdominal wall incisions because there is no communication between upper and lateral TAP spaces. (Figure 1).[43] Dual blocks combine subcostal and lateral/posterior TAP blocks, thus providing complete coverage. Four quadrant TAP blocks should be performed to have good coverage especially for any incision that goes above umbilicus.

TAP blocks only provide somatic pain relief; they therefore provide analgesia for surgical incisions, but not for visceral pain. Numerous studies show that TAP block with plain bupivacaine provided substantially better analgesia and reduced opioid consumption compared to unblocked or placebo patients for up to 24 hours.[44] TAP blocks with conventional local anesthetics including bupivacaine, ropivacaine and levobupivacaine in TAP block provide safe and effective analgesia, but only for the initial 24 postoperative hours. Long-acting local anesthetics are an alternative that might provide analgesia through the initial and most painful postoperative days.

D. Liposomal bupivacaine (Exparel; bupivacaine liposome injectable suspension, Pacira Pharmaceuticals, Inc., Parsippany, NJ USA)

Exparel is the prolonged-release formulation of the bupivacaine used for a single-shot infiltration of surgical sites or for nerve blocks. Exparel was approved by the US Food and Drug Administration (FDA) in 2011 for infiltration blocks, and in 2018 it received approval for the interscalene brachial plexus block.[45]

Liposomal bupivacaine depofoam technology is based on multiple microscopic spherical particles with many aqueous chambers separated by lipid membranes. When refrigerated, the particles are stable; but after injection of liposomal bupivacaine into soft

tissue, bupivacaine is released from the multivesicular liposomes. The components of depofoam particles are non-toxic and clinical trials have demonstrated no adverse events. Furthermore, this technology previously has been safely used in various settings and provides sustained release of bupivacaine in other target areas. Liposomal bupivacaine administration produces dose-dependent increases in plasma bupivacaine concentrations, and that the half-life of liposomal bupivacaine was almost twice that of plain bupivacaine. However, maximum plasma concentrations are no higher with plain than liposomal bupivacaine.

a. Infiltration and liposomal bupivacaine

Postsurgical pain is intense in first few days and liposomal bupivacaine may be good option for controlling post-surgical pain. Many studies have evaluated infiltration of liposomal bupivacaine. Golf et al,[46] for example, compared liposomal bupivacaine and placebo in bunionectomies. Cumulative pain scores were lower, and the time to first opioid use was significantly prolonged by liposomal bupivacaine. Hass et al.[47] compared bupivacaine and various doses of liposomal bupivacaine in hemorrhoidectomies and found progressive reductions in opioid consumption as the dose of liposomal bupivacaine increased. Postoperative opioid consumption was significantly lower in patients given 266 mg of Exparel than in those given plain bupivacaine over 12 to 72 hours postoperatively. Local infiltration of liposomal bupivacaine also reduced postoperative pain compare with plain bupivacaine. A recent meta-analysis of 10 randomized wound infiltration studies concluded that cumulative pain scores were improved with liposomal bupivacaine through 24-72 hours. First use of opioid rescue medication was also delayed, and patient were more satisfied and experienced fewer opioid-related side effects.[48]

A systematic review that evaluated liposomal bupivacaine infiltration for total hip arthroplasty showed that local liposomal bupivacaine infiltration reduced pain score, nausea and vomiting, and opioid consumption. However, this analysis was weakened by inclusion of studies with small sample sizes and others that were observational.[49] The PILLAR cohort study compared liposomal and plain bupivacaine infiltration for total knee arthroplasty and showed that 10% of patients in liposomal bupivacaine group were opioid free. Total opioid consumption and pain intensity score also less when compared to

bupivacaine group. These PILLAR study results suggest that local infiltration of liposomal bupivacaine is analgesic and reduces or even eliminates the need for opioids after total knee arthroplasty.[50] A number of studies report that liposomal bupivacaine has good efficacy and safety profiles in patients having knee, hip, and shoulder replacements.[51-61] Liposomal bupivacaine has also been effective in plastic surgical procedures including mammoplasty and abdominoplasty, and provides longer pain relief. However, dose heterogeneity and small sample sizes make these results difficult to interpret.

b. Nerve block and liposomal bupivacaine

Single-shot peripheral nerve blocks with liposomal bupivacaine have distinct advantages compared to a continuous catheter. Specifically, patients given liposomal bupivacaine will not require infusion pumps and cannot develop catheter-related infection, hematoma, or dislodgement. Because liposomal bupivacaine was only recently approved for peripheral nerve blocks, and only at one site, there is currently little information about the approach. However, Hadzic et al. compared liposomal bupivacaine to placebo for femoral nerve blocks and found lower pain score and decreased opioid consumption were reduced.[62] A retrospective analysis of peripheral nerve blocks with liposomal bupivacaine suggests that safety and the side effect profile are similar with bupivacaine and placebo.[63]

Intercostal nerve blocks with liposomal bupivacaine were evaluated after thoracic surgeries and compared with plain bupivacaine. Liposomal bupivacaine reduced hospital duration — but curiously without a reduction in postoperative pain score or opioid use.[64,65] Further studies are clearly needed to evaluate the efficacy of liposomal bupivacaine in nerve blocks.[66]

c. TAP block and liposomal bupivacaine

So far only a few trials directly compare liposomal and plain bupivacaine for TAP blocks, and there is no consensus among them. According to a Cochrane systemic review, evidence is lacking for the efficacy of liposomal bupivacaine in TAP blocks, and concludes that there is no advantage to use of liposomal bupivacaine for this indication.[67] It is important to recognize, though, that this conclusion is based on lack of evidence for benefit rather than robust evidence against. In another study, Guarre et al.[68] compared

plain and liposomal bupivacaine in TAP blocks for laparoscopic colorectal surgery. Patients treated with liposomal bupivacaine required less opioid, had earlier return of bowel function, and left the hospital sooner. Hutchins et al.[69] showed that TAP blocks with liposomal bupivacaine provided long-lasting analgesia compared to plain bupivacaine for laparoscopic-assisted donor nephrectomy, and reduced nausea and vomiting and the duration of hospitalization.[69] In contrast, Ha et al.[70] compared liposomal bupivacaine and plain bupivacaine in TAP blocks for breast reconstruction and reported no benefit.[70]

E. Rationale of the Study

The recent enhancement of conventional bupivacaine with encapsulated bupivacaine much prolongs the duration-of-action and resulting pain control with a single application. TAP blocks appear to be easier to perform (especially with ultrasound guidance), safer, relatively inexpensive, and can be used safely in patients who are anti-coagulated. However, the literature is scarce on comparison of plain bupivacaine versus liposomal bupivacaine in TAP blocks. Some clinicians therefore question the efficacy and benefit of liposomal bupivacaine for TAP blocks, especially considering the cost of liposomal bupivacaine. We therefore aim to compare the analgesic efficacy of TAP blocks with liposomal bupivacaine, plain bupivacaine, and placebo in patients who are scheduled for major abdominal surgery.

2. Study Objectives

We will prospectively compare the analgesic efficacy of TAP blocks with liposomal bupivacaine, plain bupivacaine, and placebo in patients who are scheduled for major abdominal surgery. The proposed research will have the following aims:

Primary Aims

Primary Aim 1:

To assess the relative effects of TAP blocks with liposomal bupivacaine, plain bupivacaine and placebo on opioid consumption in first 24 hours post surgery.

Hypothesis. Opioid consumption over the initial 24 hours after major abdominal surgery is less when four-quadrant TAP blocks are performed with liposomal bupivacaine and plain bupivacaine compared to placebo. Opioid consumption will be evaluated as morphine sulfate equivalents; a difference of at least 10 mg in first 24 hours will be considered to be a clinically meaningful difference.

Primary Aim 2:

To assess the relative effects of TAP blocks with liposomal bupivacaine, plain bupivacaine and placebo on opioid consumption between 24 and 48 hours post surgery.

Hypothesis. Opioid consumption between 24 and 48 hours after major abdominal surgery is less when four-quadrant TAP blocks are performed with liposomal bupivacaine than with plain bupivacaine or placebo. Opioid consumption will be evaluated as morphine sulfate equivalents; a difference of at least 10 mg will be considered to be a clinically meaningful difference.

Criteria for success will be 1) superiority of bupivacaine and exparel groups over placebo and noninferiority between plain bupivacaine and exparel groups in the first 24 hours of opioid consumption and superiority of exparel group over placebo and bupivacaine in the 24-48 hours opioid consumption.

Criterion for success of each intervention in each period.

0-24 hours: for each of bupivacaine and exparel, success will be concluded if found to be superior over placebo (i.e., less opioid consumption). As well, exparel or bupivacaine will be concluded better than the other if found superior on opioid consumption.

24-48 hours: exparel will be concluded successful if found better than both placebo and bupivacaine in the 24-48 hours opioid consumption.

Secondary Aims

Secondary Aim 1:

To assess the duration of the local analgesia (determined by pinprick and cold) in all four quadrants with liposomal bupivacaine, plain bupivacaine, and placebo after major abdominal surgery.

Hypothesis. Abdominal wall analgesia from four-quadrant TAP blocks with single-shot liposomal bupivacaine lasts longer after major abdominal surgery than the same blocks with plain bupivacaine or placebo. Our major outcome will be time from end of the block until abdominal wall sensation with both ice and pinprick recovers in at least six of eight designated locations. Two sequential evaluations will be needed to be negative and first negative time point will be accepted as the return of sensation.

Secondary Aim 2:

To compare the effect of liposomal bupivacaine, plain bupivacaine, and placebo on pain after surgery in first 72 hours or the duration of hospitalization if shorter.

Hypothesis. Pain scores over the initial 72 hours or duration of hospitalization after major abdominal surgery are lower when four-quadrant TAP blocks are performed with liposomal bupivacaine than with plain bupivacaine or placebo. Pain will be assessed on a 0-10-point scale (10 points being worst) at 4-hour intervals while patients are awake. A difference of at least 1.2 points will be considered clinically meaningful.

Secondary Aim 3:

To evaluate TAP blocks with liposomal bupivacaine, plain bupivacaine, and placebo on opioid consumption in 24 to 48 hours.

Hypothesis. Opioid consumption from the 48 to 72 hours or duration of hospitalization after major abdominal surgery is less when four-quadrant TAP blocks are performed with liposomal bupivacaine than with plain bupivacaine or placebo. Opioid consumption will be evaluated as morphine sulfate equivalents; a difference of at least 10 mg will be considered to be a clinically meaningful difference.

Tertiary

Tertiary Aim 1. To compare the effect of liposomal bupivacaine, conventional bupivacaine, and placebo on a composite of opioid-related postoperative side effects.

Hypothesis. Opioid-related side effects over the initial 72 hours or duration of hospitalization after major abdominal surgery are less common when four-quadrant TAP blocks are performed with liposomal bupivacaine than with plain bupivacaine or placebo. Opioid-related side effects will be evaluated as composite of events, and a difference of 20% in incidence will be accepted as clinically important difference.

Tertiary Aim 2. To compare the effect of liposomal bupivacaine, conventional bupivacaine, and placebo on satisfaction with their pain treatment after first 72 hours or the duration of hospitalization if shorter.

Hypothesis. Patients are more satisfied with pain management over the initial 72 hours or duration of hospitalization after major abdominal surgery when four-quadrant TAP blocks are performed with liposomal bupivacaine than with plain bupivacaine or placebo.

Tertiary Aim 3. To assess total and specific costs of hospital care in patients receiving TAP with liposomal bupivacaine vs. those with plain bupivacaine following abdominal surgery.

Tertiary Aim 4. To compare the effects of TAP blocks with liposomal bupivacaine, plain bupivacaine and placebo on patients' pain with movement for 72 hours/discharge surgery.

Hypothesis. Pain scores with movement over the initial 72 hours or duration of hospitalization after major abdominal surgery are lower when four-quadrant TAP blocks are performed with liposomal bupivacaine than with plain bupivacaine or placebo. Pain will be assessed on a 0-10-point scale (10 points being worst) at 12-hour intervals while patients are elevating their leg. A difference of at least 1.2 points will be considered clinically meaningful.

Tertiary Aim 5. To compare the effects of TAP blocks with liposomal bupivacaine, plain bupivacaine and placebo on patients' mobility for 72 hours/discharge surgery.

Hypothesis. Total amount of mobilization over the initial 72 hours or duration of hospitalization after major abdominal surgery are higher when four-quadrant TAP blocks are performed with liposomal bupivacaine than with plain bupivacaine or placebo.

3. Method and Study Design

A. Study Overview

We propose a randomized double-blind trial comparing TAP blocks with liposomal bupivacaine, plain bupivacaine, and placebo in patients having elective abdominal surgery. The study will be performed at various Cleveland Clinic hospitals with IRB approval and written consent from patients. Study will be registered at ClinicalTrials.gov website before the first patient is enrolled.

B. Setting and Population

Inclusion criteria:

(1) Written informed consent;

(2) 18-85 years old;

(3) ASA Physical Status 1-3;

(4) Scheduled for elective open or laparoscopic-assisted abdominal surgery;

(5) Anticipated hospitalization of at least three nights;

(6) Expected requirement for parenteral opioids for at least 72 hours for postoperative pain;

(7) Able to use IV PCA systems.

Exclusion criteria:

(1) Hepatic disease, e.g. twice the normal levels of liver enzymes;
(2) Kidney disease, e.g. twice the normal level of serum creatinine;
(3) Bupivacaine sensitivity or known allergy;
(4) Women who are pregnant or breastfeeding;
(5) Anticoagulants considered to be a contraindication for TAP blocks;
(6) Surgeries with high port sites;
(7) Weight <70 kg.

C. Withdrawal Criteria

Patients will be free to withdraw from study at any time. Patients will also be removed from study at any time for adverse events, or deemed necessary for patient safety.

D. Protocol

After eligibility is confirmed, patients will receive complete information about the study both verbally and in writing. Informed consent will be obtained from the patients prior to randomization and study-specific procedures.

Randomization will be based on computer-generated codes and use random-sized blocks. Allocations will be concealed until the morning of surgery where they will be provided by a web-based system. Randomization will be stratified by study site and chronic opioid use, defined by opioid use for more than 30 consecutive days within three preoperative months, at a daily dose of 15 mg or more of morphine or equivalent. Randomization will also be stratified according to anticipated type of surgery (open vs. laparoscopic-assisted). Clinicians doing the blocks will not be involved in data collection and all the evaluators will be blinded to group allocations.

All blocks will be performed preoperatively or after induction of anesthesia by attending anesthesiologists or regional anesthesia fellows who are experienced in TAP blocks. Premedication will be administered at the discretion of the attending anesthesiologist and standard monitors will be used. Patients will be given 1 g oral acetaminophen an hour before surgery, and an additional 500 mg every 6 hours for 72 hours after surgery starting with oral intake.

Patients will be randomly assigned to: 1) 4-quadrant TAP block with liposomal bupivacaine; 2) 4-quadrant TAP block with plain bupivacaine; or, 3) placebo (normal saline). An in-plane ultrasound will be guide TAP blocks. Two subcostal injections will be applied by placing the probe midline and then moving lateral along the subcostal margin identifying area between the rectus abdominis sheath and the transversus abdominis muscle. The lateral two TAP block injections will be applied in the midaxillary line between

the thoracic cage and iliac crest between external oblique and transversus abdominis muscles. Once the target area is positioned, the following injections will be given, based on randomization:

Liposomal bupivacaine. 40 ml of plain bupivacaine 0.25% will be mixed with 20 ml liposomal bupivacaine and 20 ml of saline. 20 ml of the mix will be injected at each location of the 4-quadrant TAP block.

Plain bupivacaine group. 50 ml of plain bupivacaine 0.5% will be combined with 30 ml of normal saline making a total of 80 ml. 20 ml will be injected at each location of the 4-quadrant TAP block.

Placebo group; patients will receive total of 80 ml of normal saline, injected 20 ml in each of the four-quadrant sites.

General anesthesia will be induced using propofol or etomidate, fentanyl, and rocuronium to facilitate intubation. Anesthesia will be maintained with sevoflurane or isoflurane, along with opioids and muscle relaxants as clinically indicated. However, intraoperative analgesic use will be limited to fentanyl, a short-acting opioid.

Postoperatively, patients will be given intravenous patient-controlled analgesia and nurses will be free to give additional opioid as clinically indicated. Hydromorphone will be the default drug, but fentanyl will be substituted if necessary. Clinicians blinded to trial drug will adjust analgesic management as necessary in an effort to keep verbal response pain scores (details below) <4 points on a 0-10 scale, with 10 being worst pain. When patients no longer need PCA, they will be switched to as-needed hydromorphone or fentanyl.

A single dose of dexamethasone (4-8 mg) will be given to all patients for PONV prophylaxis, and inhaled steroids will be permitted as necessary to treat reactive airway disease. The use of non-steroidal anti-inflammatory drugs and gabapentinoids will be allowed as part of the ERAS approach (enhanced recovery after surgery) according to hospital's clinical practice. Other opioid-sparing medications such as ketamine and lidocaine patches will not be permitted through the initial 72 postoperative hours. Vital

signs and patient activity will be continuously monitored and recorded with a wireless monitor (ViSi mobile, Sotera Wireless, San Diego, CA). Monitoring will be started about 30 minutes after arrival in the postanesthesia care unit and continued for 72 hours while patients remained hospitalized. Clinicians will be blinded to continuous monitoring data; clinical decisions therefore will be guided by routine intermittent vital signs which were typically obtained at 4-hour intervals.

Patients will be allowed to receive prophylactic anti-emetic (first choice ondansetron) intraoperatively based on the risk assessment for nausea and vomiting. Postoperative anti-emetics for symptomatic treatment will also be allowed; again ondansetron will be the first choice.

E. Measurements

Demographic data to be obtained includes height (cm), weight (kg), age (yr), sex, (ASA) physical status, self-declared ethnicity, and the specific type of procedure will be recorded. Patients will be questioned about tobacco and alcohol use, and about illegal drug use. They will also be asked about their medical history including pulmonary disease, kidney disease, diabetes mellitus, neurological disease, chronic pain conditions, previous surgery or stent placement, and medications. Available preoperative laboratory tests and medication list will be recorded. Preoperative pain scores and opioid use will be recorded. Patients excluded for any reason including technical considerations or contraindications will be recorded.

All the procedures for the ultrasound guided TAP blocks will be recorded to the ultrasound and two blinded independent adjudicators will evaluate the success of the blocks. Blocks will be accepted as successful if 3 out of 4 locations were done correctly according to adjudicators.

***Primary Outcome* 1**

Opioid requirements will be measured as the total amount of opioids (converted to morphine sulfate equivalents) used during the first 24 postoperative hours after surgery. Use of PCA and discontinuation will be recorded.

Primary Outcome 2

Opioid consumption will be measured as morphine equivalents between 24-48 hours.

To evaluate TAP blocks with liposomal bupivacaine, plain bupivacaine, and placebo on opioid consumption in 24 to 48 hours. Use of PCA and discontinuation will be recorded.

Secondary Outcome 1

The duration of the local anesthetic effect (determined by pinprick and cold) will be evaluated in all four quadrants. The evaluation will be made in eight locations, three in each side and two in midline. The first will be below the subcostal margin at midclavicular line, the second will be on the midclavicular line between the thoracic cage and iliac crest level of umbilicus, the third will be below umbilicus on the same line. The same sites will be evaluated on the contralateral side. There will be two more locations on midline. The first will be midway between umbilicus and xiphoid, and the second will be midway between umbilicus and midpoint of a line drawn between iliac crests.

Cold tests will be performed by using ice contained in a clean nitrile glove, first applied to the patient's forearm where they will be asked to describe how it feels to confirm ice cold. Then the same ice-filled glove will be applied to the same 8 points on the abdomen described above, asking the patient to confirm "yes" when they feel cold equivalent or greater to that on their forearm. Pinprick will be evaluated by calibrated force of 256 mN and a flat contact area of 0.2 mm in diameter using a stimulator (PinPrick Stimulator Set, MRC Systems, Heidelberg, Germany).

The initial measurement will be in the preanesthesia care unit, prior to block administration. The first postsurgical evaluation will be performed within 5-30 minutes of the patient arriving in the post-anesthetic care unit (PACU) or the intensive care unit (ICU), whichever is applicable. Two further assessments will be performed in PACU/ICU/regular

nursing floor at one hour intervals. Subsequently, assessments will be performed at 2 hourly intervals (x3) then at 12 hours postop (defined as patient leaving the OR), 18 hours postop, 24 hours postop, 30, 36 hours postop, 48 hours postop, 60 hours postop, 72 hours postop (when patients are not sleeping). Testing will continue until abdominal wall sensation returns or 72 hours have elapsed since surgery. We will consider sensation recovered when patients feel both ice and pinprick in at least 6 of the 8 designated test locations. If the TAP block did not initially cover all eight locations, sensation will be considered recovered when patients sense ice and pinprick at ≥75% of the covered points (i.e., 5/7, 5/6, 4/5, 3/4, 3/3, etc.). Two sequential evaluations will be needed to be negative and first negative time will be accepted as the return of sensation.

Secondary outcome 2

Pain Scores after surgery will be measured using a Verbal Response Scale (VRS). VRS is a scale from 0 to 10 where 0 signifies no pain and 10 signifies worst pain ever experienced. The VRS will be recorded at the same intervals as cold and pinprick sensation assessment described in *secondary outcome 2* above and thereafter at 4-hour intervals while patients are awake for 72 hours.

Secondary outcome 3

Opioid consumption will be measured as morphine equivalent in first between 48-72 hours.

To evaluate TAP blocks with liposomal bupivacaine, plain bupivacaine, and placebo on opioid consumption in 48 to 72 hours. Use of PCA and discontinuation will be recorded.

Tertiary Outcome 1

A composite of opioid-related side effect after surgery will be recorded for 72 hours. Components of the composite include nausea, vomiting, ileus, constipation, pruritus, itching, urinary retention, use of antiemetics or naloxone or antihistamines.

Tertiary Outcome 2

Patients will be asked to rate their satisfaction with pain management at using a 0-10 point scale at 72 hours or upon discharge if earlier**.**

Tertiary Outcome 3

Total cost of hospital care and specific care costs will be estimated from data in the electronic medical records database. Data obtained from electronic medical records will include: operation time, surgery type, intraoperative opioid consumption, postoperative opioid consumption in PACU and in ward, breakthrough pain medication requirements, pain scores in PACU and ward, requirement of oxygen in PACU and ward, pruritus, requirement of antihistaminic medications, requirement of naloxone, itching, ambulation time, flatus, ileus, bowel movements (first time documented), constipation, length of stay and any side effects or complications.

Tertiary Outcome 4

Pain Scores with movement after surgery will be measured using a Verbal Response Scale (VRS). The VRS will be recorded every 12 hours by asking patient to lift their legs up to 72 hours postop or until discharge, whichever is sooner. The patient will also be asked to report their VRS at rest prior to leg raise for reference.

Tertiary Outcome 5.

Patient's mobility will be obtained from VISI monitoring device for 72 hours/discharge surgery

F. Data Analysis

Randomized groups will be compared for baseline balance using standard descriptive statistics and the standardized difference (difference in means or proportions divided by the pooled standard deviation).

Primary Outcomes. *Opioid consumption*. The following tests for superiority on opioid consumption will be conducted (see type I error control below): 1) 0-24 hours post-surgery: compare each of exparel and plain bupivacaine to placebo; and 2) 24-48 hours post-surgery: compare exparel to each of plain bupivacaine and placebo. Groups will be compared using linear regression on log-transformed morphine equivalents, with results reported as ratio of geometric means between each pair of interventions.

Type I error control across Primary outcomes 1 and 2. We will use a parallel gatekeeping procedure to control the type I error at 5% across the 2 primary outcomes. The 2 comparisons for the 0-24 hour period will constitute Set #1, and the 2 comparisons for the 24-48 hour period will constitute Set #2. Within each set we will use the Holm-Bonferroni (HB) multiple comparison procedure among the two comparisons. If either test in the first Set is significant (HB: significance criterion of 0.025 for smaller P-value and 0.05 for the larger), analysis will continue to Set #2. Otherwise, Set #2 will not be analyzed. If analysis proceeds to Set #2, the overall alpha for Set #2 will be 0.05 x proportion of significant tests in Set #1 (i.e., Set #2 alpha = either 0.05 x 1 or 0.05 x ,5 = 0.025).

Secondary Outcomes.

*Time to return of sensation***.** We will compare the 3 randomized groups on the time to detection of return of sensation (see above; i.e., when patients feels both ice and pinprick in at least 6 of the 8 designated test locations, or ≥75% of the covered points if the TAP block did not initially cover all eight locations) using a time-to event Kaplan-Meier analysis and log-rank test, and comparing patients on the estimated median time to return of sensation. If all patients do have return of sensation (as expected), the analysis will be equivalent to a Wilcoxon rank sum test, and so this test and the corresponding Hodges-Lehman estimator of median difference (CI) will be reported as a sensitivity analysis. The significance criterion for each of the 3 comparisons will be 0.05/3 = 0.0167 to control the type I error at 0.05 for the primary outcome.

Pain score. We will compare the 3 randomized groups on mean pain score over the first 72 hours using a linear mixed effects model in which we adjust for within-subject

correlation assuming an autoregressive correlation structure (or unstructured or other, whichever fits best; but making sure to also account for the differences in timing between the measurements) with fixed effects of treatment and categorical time. While we will assess the treatment-by-time interaction, main results will be reported collapsing over time regardless of a significant interaction.

Opioid consumption 48-72 hours. This will be analyzed using linear regression as with the primary outcomes.

Type I error will be controlled at 0.05 for secondary outcomes by using a significance criterion of 0.05/3=0.017 for each outcome.

Tertiary Outcomes.

Groups will be compared on the collapsed composite of opioid-related side effects in the first 72 hours after surgery using chi-square tests. Groups will be compared on satisfaction with pain management at using a 0-10 point scale at 72 hours, or upon discharge if earlier, using the Kruskal-Wallis test overall and Wilcoxon rank sum test between interventions.

Economic Analysis. Finally, if a treatment effect between the 2 local anesthetic TAP blocks is detected, we will conduct a cost-effectiveness analysis estimating the incremental cost-effectiveness ratio (ICER) as the mean difference in costs divided by the mean difference in the primary outcome of time to return of sensation [or an analogous ratio using summaries which best fit the distribution of the data]. Total cost of hospital care and specific care costs will be estimated from data in the electronic medical records database. Data obtained from electronic medical records will include: operation time, surgery type, intraoperative opioid consumption, postoperative opioid consumption in PACU and in ward, breakthrough pain medication requirements, pain scores in PACU and ward, requirement of oxygen in PACU and ward, pruritus, requirement of antihistaminic medications, requirement of naloxone, itching, ambulation time, flatus, ileus, bowel movements (first time documented), constipation, length of stay and any side effects or complications.

Interim Analyses. We will use a group sequential design to conduct interim analyses at each 25% of the planned enrollment to assess efficacy and futility of the intervention using a gamma spending function. Specifically, we will maintain the overall alpha level (monitoring efficacy) at 0.05 using gamma parameter of -4 [similar to O'Brien Fleming], and power at 90% (monitoring beta, type II error) using gamma parameter of 0 [more aggressive, similar to Pocock]. Under the alternative hypothesis (assuming a true 50% relative reduction in the primary outcome) the cumulative probability of crossing an efficacy (and futility in parentheses) boundary at the 1st through 4th analyses will be 0.09 (0.025), 0.39 (0.05), 0.75 (0.075) and 0.90 (0.10) as shown in **Figure 1.**

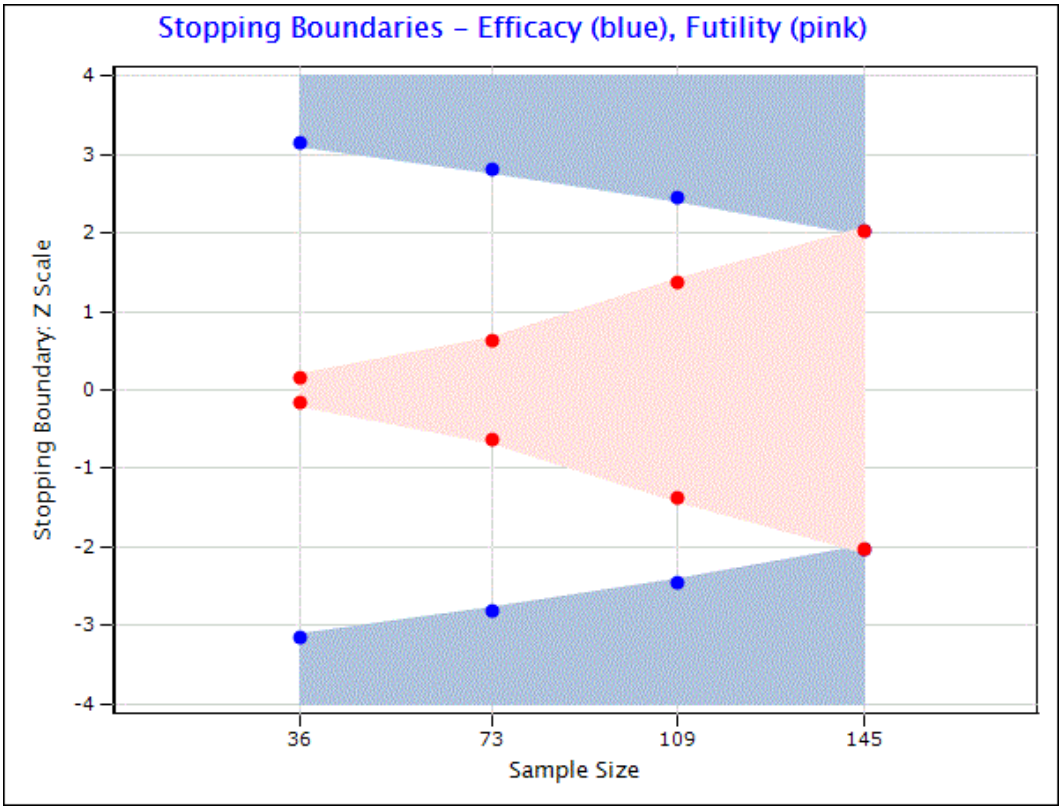


Figure 1. Group sequential stopping boundaries as a function of sample size. Pink region represents futility. Lower blue represents efficacy of NAC, upper blue represents harm. Y-axis represents the treatment effect (Z= difference in means divided by standard error).

G. Sample Size Considerations

We plan the study to have 90% power at the overall 0.05 significance level to be able to detect a relative improvement of 40% or more in mean opioid consumption(i.e., ratio of geometric means of 0.60) between any of the 3 interventions, assessing separately for 0-24 hours (primary outcome #1) and 24-48 hours (primary outcome #2) postoperatively. Assuming a coefficient of variation (CV = SD/,mean) for opioid consumption of 0.85 [since the outcome is expected to be log-normal], the required sample size to will be 67 per group or 201 total. After adjusting for the interim analyses the maximum sample size will be 79 per group or a total of 237. Alternatively, for example, a total (maximum) sample size of 722 would be required to detect a more modest 25% reduction in the mean.

Internal pilot assessment of variability. At the second interim analysis, we will conduct an internal pilot study to assess the observed variability in the primary outcome and the related coefficient of variation (CV). If the CV is larger than planned in the protocol, we will resize the study accordingly, keeping everything else the same. For example, if the observed CV is 1.0 (instead of 0.85), the new maximum sample size would be a total of 298 patients to detect the same 40% relative reduction in the outcomes. The internal pilot assessment will not affect the type I error of the study nor alter the effect size of interest.

Adaptive design option. At the 3rd interim analysis we may consider an adaptive design in which the study is repowered for a smaller but still clinically important treatment effect. Specifically, if the conditional power at the 3rd look is between 30% and 75%, the DSMB (or Executive Committee) we will consider resizing the study to have 90% power to detect a relative reduction as small as 20% (i.e., a ratio of geometric means of 0.80). [71]

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