Version #4 8/15/2019
NCT03541941

Three-Armed Double-Blind Randomized Controlled Clinical Trial: Exparel® vs. Bupivacaine Hydrochloride vs. Placebo for Transversus Abdominis Plane Blocks During Open Retromuscular Ventral Hernia Repair

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INTRODUCTION

Reduction of postoperative pain is a concern for all surgeons, as higher levels of pain are associated with decreased quality of life, prolonged convalescence, greater consumption of narcotic pain medications and prolonged length of stay.[1-3] Abdominal wall reconstruction often requires major midline laparotomies, myofascial releases and extensive dissection into the retromuscular, preperitoneal and retroperitoneal spaces, and therefore, not surprisingly, is associated with significant postoperative pain. In order to improve postoperative pain management and minimize opioid consumption and its associated side effects, multimodal approaches to postoperative analgesia have been used with increasing frequency in many fields of surgery[4] and are important components of protocols for enhanced recovery after surgery (ERAS). Such approaches have the objective of improving pain control using multiple classes of medications, ultimately minimizing opioid use [5]. One of the possible interventions of such multimodal approaches is the transversus abdominis plane block (TAP block), a regional anesthetic technique that blocks the neural afferents of the anterolateral abdominal wall.[4] Several studies have evaluated the utility of TAP blocks for postoperative analgesia after abdominal surgery and found a significant reduction in opioid consumption, pain scores and shortened length of stay.[6] Different local anesthetics can be injected to perform a TAP block, including lidocaine, bupivacaine hydrochloride, liposomal bupivacaine, and ropivacaine.[7] The utility of TAP blocks with bupivacaine hydrochloride in the management of acute postsurgical pain is limited by its short duration of action [8]. Exparel® (Pacira Pharmaceuticals, San Diego, California) is a bupivacaine liposomal injectable suspension marketed to diffuse over an extended 72 hour period. [9] The joint administration of Exparel® and bupivacaine hydrochloride has been shown in a placebo-controlled randomized controlled trial to reduce pain

immediately following open reduction internal fixation [10]. Fayezizadeh et al. suggested that Exparel® is efficacious in not only reducing acute narcotic requirements but also hospital length of stay following open abdominal wall reconstruction [4]. In addition, a Phase IV, prospective, single-center trial of 43 patients following ileostomy reversal surgery has suggested that despite its diffusion over only a 72-hour period, Exparel® may even be associated with decreased 30-day postsurgical opioid use [11]. The ability of Exparel® to produce extended relief is further supported by a multicenter study [12]. Despite the ability of both Exparel® and bupivacaine hydrochloride to reduce pain, the additional costs of Exparel® are irrefutable. Bupivacaine hydrochloride costs $1.15 per 20 ccs of the product while Exparel® costs $285 for the same amount [13].

We have incorporated the administration of Exparel® into an enhanced multifactorial recovery after surgery (ERAS) pathway designed to hasten patient recovery postoperatively [14]. A preliminary retrospective review of 30 patients undergoing our ERAS initiative revealed a mean hospital length of stay of 5.14 days [15], which is a reduction versus historical controls [16]. Although the efficacy of Exparel® has been assessed in a variety of studies with orthopedic, colorectal and gynecological surgery populations, high-quality scientific data evaluating Exparel® in the abdominal wall reconstruction literature is lacking. Furthermore, a recent Cochrane review [17] concluded that there is lack of data to support or refute the administration of Exparel® as a peripheral nerve block for postoperative analgesia since the current literature on Exparel® suffers a limited number of trials, with a small number of participants and inconsistency of results.

To determine if Exparel® influences on opioid requirements, postoperative pain levels, hospital length of stay and patient-reported quality of life following ventral hernia repair, we

propose a registry-based randomized clinical trial through the Americas Hernia Society Quality Collaborative (AHSQC). The AHSQC is a multicenter, nationwide quality improvement effort with the mission of improving the quality of hernia care [16]. We hypothesize that a TAP block with Exparel®, performed intraoperatively by a surgeon during open ventral hernia repair with mesh placed in retromuscular position, will result in decreased opioid requirements, reduced immediate and extended postoperative pain scores, shorten length of hospital stay, and improved quality of life when compared to a TAP block with Bupivacaine hydrochloride or placebo (normal saline), performed in the same manner and in the same population.

The aims of this study are:

Specific Aim #1: To determine if intra-hospital opioid requirements over initial 72 hours differ following the administration of Exparel®, Bupivacaine hydrochloride, or placebo (normal saline) through a TAP block during open ventral hernia repair with retromuscular mesh placement. Opioid consumption will be assessed by measuring the cumulative dose of opioids administered through intravenous and oral preparations. Intravenous opioids will include all opioids infused through a patient-controlled analgesia device (PCA) and intravenously as a rescue medication for breakthrough pain. Specific time points for assessments are: at post-anesthesia care unit (PACU/POD0), and daily during the hospital stay up to a maximum of 7 days. Opioid requirements will be recorded and converted into morphine equivalents for standardization. In addition, we aim to record and analyze: (1) amount of opioids administered intraoperatively by the anesthesiologist, (2) cumulative dose of opioids during the first 7 days of hospital stay and (3) time to first oral opioid use.

Specific Aim #2: To determine if immediate and extended pain scores differ following the administration of Exparel®, Bupivacaine hydrochloride, or placebo (normal saline) through a

TAP block during open ventral hernia repair with retromuscular mesh placement. Immediate time points include while patients are at PACU/POD0, and daily during the hospital stay up to a maximum of 7 days. An extended time point includes 30-days postoperatively.

Specific Aim #3: To determine if hospital length of stay differs following the administration of Exparel®, Bupivacaine hydrochloride, or placebo (normal saline) through a TAP block during open ventral hernia repair with retromuscular mesh placement.

Specific Aim #4: To determine if 30-day patient-reported quality of life (PRQOL) scores differ following the administration of Exparel®, Bupivacaine hydrochloride, or placebo (normal saline) through a TAP block during open ventral hernia repair with retromuscular mesh placement.

STUDY DESIGN

As in previous randomized controlled trials executed by our research group, the AHSQC will serve as a platform for data collection. Additional data not captured by the AHSQC will be recorded by a trained study coordinator or research fellow and uploaded into Research Electronic Data Capture (RedCAP®). Baseline and intraoperative variables, as well as some of our outcomes of interest (30-day pain scores, hospital length of stay, PRQOL), are already captured within the AHSQC database, allowing for follow-up and data capture with minimal additional effort outside that of routine care (11).

This will be a double-blind, 3-arm, randomized controlled trial with a treatment 1: treatment 2: control allocation ratio of 1:1:1. No important changes to the methods after trial commencement are anticipated. We anticipate that this will be a single-institutional study of patients undergoing elective open ventral hernia repair at Cleveland Clinic Comprehensive

Hernia Center (Main Campus, Cleveland Clinic Foundation, Cleveland, Ohio, USA) performed by 4 staff surgeons: Dr. Michael J. Rosen (PI), Dr. Steven Rosenblatt (co-I), Dr. Ajita Prabhu (co-I) and Dr. David Krpata (co-I). Nonetheless, we do not discard to turn this trial into a multi-institutional trial in the future. No important changes to the methods after trial commencement are anticipated. No interim analyses will be performed, and no stopping guidelines are needed since the interventional arms of this study are already currently performed at our institution, and we do not anticipate adverse events requiring study suspension.

Inclusion criteria are all adult patients (at least 18 years of age) undergoing open, elective, clean or clean-contaminated (wound classification), ventral hernia repairs with mesh placed in retromuscular position. We have no restrictions on hernia size, and the indication of the operation will be at the discretion of the attending surgeon. Exclusion criteria include: (1) patients unable to give informed consent, (2) patients with allergy, hypersensitivity or contraindication to bupivacaine, (3) patients with history of chronic liver disease with moderate or severe impairment in liver function defined as a Child-Pugh class B or C (4) patients with a history of chronic renal insufficiency on dialysis; (5) patients who are considered chronic opioid users, defined as daily or near daily use of opioids for at least 90 days in the past year and (6) patients from vulnerable populations as further detailed in this protocol. Patients scheduled for minimally invasive hernia repairs or open ventral hernia repairs with mesh placed in a position other than retromuscular will also be considered exclusion criteria. Also, open repairs performed through a different incision than the standard midline approach will also be considered exclusion criteria.

OUTCOMES OF INTEREST

Primary outcomes of Interest

Primary outcomes of interest are opioid requirements and pain scores over initial 72 hours of the postoperative period. Opioid requirements will be assessed by measuring the cumulative dose of opioids administered intravenously (infused through a patient-controlled analgesia device as well as the quantity of opioids administered intravenously as rescue, if needed) and the quantity of opioids administered through oral preparations. This will be assessed at time points: at day of surgery (while patients are at PACU or the nursing floor), at postoperative days 1, 2 and 3. Additional time points include daily assessments during the rest of the hospital stay up to a maximum of 7 days. The total dose of opioids used at each time point will be recorded and converted into morphine equivalents for standardization and analysis. We will record the cumulative dose of opioids from 0 hours to 72 hours after the operation and for the total hospital length of stay (up to a maximum of 7 days). In addition, we aim to record the dose of opioids administered intra-operatively by the anesthesiologist, time for first oral opioid dose over the first 72 hours (discontinuation of PCA), and the percentage of patients not requiring opioids over the first 72 hours.

Pain scores will be determined using a 100mm visual analog scale (VAS). The VAS is a 100mm horizontal line with two endpoints: 0 (no pain) and 100 (worst imaginable pain). While in the hospital, subjects are to assess, “How much pain are you experiencing right now?” Pain scores will be assessed at baseline during preoperative evaluation, at day of surgery (PACU or nursing floor), at postoperative days 1, 2 and 3. Additional time points include daily assessments during the rest of the hospital stay up to a maximum of 7 days.

Additional pain scores will be obtained using the Patient-Reported Outcome Measurement Information System (PROMIS) Pain Intensity 3a survey, which is part of the

AHSQC patient-reported outcomes, at baseline and postoperative day 30 (± 15 days). The PROMIS pain intensity questionnaire is a National Institutes of Health-developed validated tool that focuses on patient-reported outcomes of pain characteristics. This survey will be completed by patients in person during enrollment, and either in person, by telephone interview or virtual visit for 30-day follow-up, if a patient is unable to come to the clinic during the defined time frame (30days±15days).

Secondary Outcomes of Interest

Secondary outcomes of interest include the length of hospital stay and Patient-Reported Quality of Life (PRQOL). Both information is already routinely collected through the AHSQC. Length of hospital stay will be recorded in days. PRQOL will be assessed using the HerQLes survey. [20] The HerQLes is a 12-item, validated, a hernia-specific survey that assesses quality of life through abdominal wall function after ventral hernia repair. HeQLes scores will be assessed at baseline and 30 days after the operation. This tool is also part of the patients reported outcomes of the AHSQC.

Additional Outcomes of interest

Pertinent baseline patient demographics, hernia variables, intraoperative details and 30-day outcomes including surgical and medical complications are also captured routinely for all patients in the AHSQC, as a standard of care.

STUDY PROCEDURES

The interventions are:

- Treatment 1- Administration of a solution of Exparel® combined with Bupivacaine Hydrochloride 0.25% and normal saline, through a bilateral TAP block performed intraoperatively by the attending surgeon, during open ventral hernia repair;
- Treatment 2: Administration of a solution of Bupivacaine Hydrochloride 0.25% and normal saline, through a bilateral TAP block, performed intraoperatively by the attending surgeon, during open ventral hernia repair ;
- Control (Placebo): administration of normal saline through a bilateral TAP block performed intraoperatively by the attending surgeon, during open ventral hernia repair. These formulations were suggested by the fabricant and are already under study in other protocol investigating Exparel at our institution.

INTERVENTION 1 (EXPAREL® + BUPIVACAINE HYDROCHLORIDE 0.25%)	INTERVENTION 2 (BUPIVACAINE HYDROCHLORIDE 0.25%)	CONTROL GROUP (PLACEBO)
• 20cc of Exparel® • 60cc Bupivacaine Hydrochloride 0.25% without epinephrine • 40cc Normal Saline Final Volume: 120cc	• 60cc Bupicavaine Hydrochloride 0.25% without epinephrine • 60cc Normal Saline Final Volume: 120cc	• 120cc NORMAL SALINE

Randomization

Patients will be randomized using a computer-generated random allocation sequence, by the investigational pharmacy personnel. The random allocation sequence will be implemented with REDCap®, where a randomization allocation table will be generated and uploaded into REDCap® by the study statistician listed in this protocol. Randomization will occur during the operation at the end of adhesiolysis, and at the beginning of abdominal wall reconstruction, to allow for sufficient time for the investigational pharmacy to prepare and dispense the assigned intervention. This study will be double-blinded since patients will be blinded to their assigned intervention until their participation in the study is complete, and also surgeons will be blinded to the intervention assigned to the subject. Only the investigational pharmacy will be aware of the

assigned intervention and this information will be stored in the appropriate randomization platform in REDCap. The study coordinator and other research personnel who will be abstracting opioids doses and pain scores from patients will also be blinded to the intervention that was assigned to patients.

Surgical Procedure

All patients will undergo the same operation, under a standard of care protocol. Our surgical approach to open ventral hernia repair with retromuscular mesh placement is further detailed. Skin preparation, hair removal, perioperative antibiotics and venous thromboembolism prophylaxis will be performed per Surgical Care Improvement Project protocol guidelines. The procedure will be performed through a midline incision. Upon entering the abdominal cavity, all adhesions between intra-abdominal contents and the anterior abdominal wall are routinely lysed using sharp dissection. When present, hernia contents are reduced back to the cavity. At the end of adhesiolysis, the surgeon will ask the OR nurse to contact the investigational pharmacy via telephone, who will randomize the subject. The investigational pharmacy will be responsible for preparing and dispensing the assigned intervention. The OR nurse will receive the drug from the investigational pharmacy in a standardized bag and will dispense it to the surgeon at the time of the TAP block. Neither the surgeon nor other members of the surgical team will be informed about which of the interventions were assigned to the specific patient. Electronic medical records will contain the information: “Patient was randomized and assigned to receive intervention according to randomization performed by investigational pharmacy.”

Retromuscular hernia repair is performed initially incising the posterior rectus sheath just lateral to the linea alba. The release will be performed at least 5 cm above and below the fascial

defect, and retrorectus dissection is carried out laterally in the direction of the linea semilunaris. If deemed necessary, a posterior component separation will be performed by incising the posterior lamella of the internal oblique, dividing the fibers of the transversus abdominis muscle and dissecting the preperitoneal and retroperitoneal spaces of the lateral abdominal wall laterally.

At the end of the myofascial release, the assigned intervention drug will be dispensed in syringes to the surgeon who will perform the perform a TAP block under direct visualization.

The TAP block

Injections of the designated drug (group 1, 2 or 3) will be performed under direct visualization by the attending surgeon, in 5 vertical levels, to the thoracoabdominal nerves (from T7 to T11).

Other details relating to administration will be per manufacturer's instructions (4). The posterior sheath will be reapproximated, and a standard piece of polypropylene mesh will be placed in the retromuscular space.

Mesh type will be defined by the surgeon intraoperatively according to the patient and hernia-specific variables. Mesh fixation will be performed circumferentially using mechanical sutures. Closed suction drains will be placed above the mesh and in the subcutaneous space, and the timing of removal will be based on the surgeon's standard practice. Fascial closure and management of wound dressings will also follow the surgeon's standard practice.

Multimodal Pain Management

For postoperative analgesia, all patients will also receive a patient-controlled analgesia (PCA) device according to the standard of care; **preferably:**

- Hydromorphone HCL 0.5mg/ml (Dilaudid®, Purdue Pharmaceuticals, Stamford, CT) in 100ml of normal saline, with no basal rate infusion, a patient bolus dose of 0.2-0.4mg, bolus interval of 6 minutes (maximum 10 doses per hour).

In case there is a contraindication to Hydromorphone, alternative PCA regimens can be:

- Morphine 1mg/ml in 100ml of normal saline, with no basal rate infusion, patient bolus of 1mg, bolus interval of 6 minutes (maximum 10 doses per hour) or,
- Fentanyl 20mcg/ml in 100ml of normal saline, with no basal rate infusion, a patient bolus of 20mcg, bolus interval of 6 minutes (maximum 10 doses per hour).

No epidural analgesia will be administered.

In addition, as part of the multimodal analgesia protocol for our enhanced recovery after surgery pathway, patients will also receive the following medications:

Acetaminophen	1G every 6 hours, after initiation of oral intake
Gabapentin	300mg every 8 hours, after initiation of oral intake
Oxycodone	5mg every 3 -4 hours as needed in the transition of weaning PCA, and after PCA has been discontinued

Although administration of Ketorolac Tromethamine (Toradol®, La Roche Inc.) is a part of the multimodal analgesia protocol of our ERAS pathway, its usage is according to patient age, comorbidities, renal function and ultimately at surgeon's discretion, and therefore, it will not be included in the postoperative pain management of the patients included in this study to avoid introducing bias to our results.

Rescue medication

To ensure the comfort and adequate pain postoperative pain control, additional intravenous or oral opioids are allowed in the protocol, to be administered for breakthrough pain (as needed). Subjects should only receive rescue medication upon request, and for pain control. Options for postsurgical rescue medication are:

- Hydromorphone 0.5mg/ml, 0.4mg administered intravenously; Dose can be repeated every 15 minutes, up to 3 doses. The sequence can be repeated every 6 hours if needed.
- Morphine 1mg/ml, 1 to 2mg administered intravenously; Dose can be repeated every 15 minutes, up to 3 doses. The sequence can be repeated every 6 hours if needed.
- Fentanyl 20mcg/ml, 25 to 50mcg administered intravenously; Dose can be repeated every 15 minutes up to 3 doses. The sequence can be repeated every 6 hours if needed.

No other pain medications will be allowed in this protocol. All other aspects of postoperative management are standard of care and will occur at surgeon's discretion and guided by current best practices of the Cleveland Clinic Comprehensive Hernia Center.

Exclusions from the study during participation

Patients will be excluded from participation in the trial if:

- Remain intubated for more than 12 hours after the end of operation due to any reason since important part of the assessments will not be performed
- Experience any medical event that demands management with opioid medications that are used not exclusively for pain management (for example, patients placed in mechanical ventilation who receive continuous infusion of opioids)

Also, patients can be excluded from the study at any moment during the trial if they withdraw consent or according to clinical judgment of the PI.

ANTICIPATED TIME FRAME

Estimated patient accrual time is 1 year with data collection to occur over 30 days from randomization of each patient. Data analysis and manuscript production will occur within 6 months of the completion of data collection.

PATIENT RISKS AND DISCOMFORTS

As with any surgical procedure, patients may experience pain, bleeding, and discomfort. Common occurrences following hernia repair include seroma, hematoma, inflammation, wound dehiscence, and infection. Risks of Bupivacaine Hydrochloride include allergic reactions, arrhythmias, chest pain or pressure, dizziness, confusion, restlessness, tinnitus, blurred vision, dyspnea, seizures, nausea, emesis, and lethargy. Risks of Exparel® include nausea, vomiting, constipation, as well as (rarely) seizures and cardiac arrest. Patients receiving placebo intraoperatively will not necessarily experience higher levels of pain, as all individuals,

regardless of intervention arm, will be provided a multimodal pain management regimen with patient-controlled analgesia postoperatively.

PATIENT BENEFITS

There are no direct benefits to subjects for participation in this study. Subject participation will, however, help physicians and hospital administrators better understand the outcomes of Exparel® use concerning postoperative pain management and its influence on opioid consumption, hospital length of stay and quality of life.

COSTS TO THE SUBJECTS

There are no extra costs to the subjects associated with this research endeavor. Procedures related to preoperative evaluation, hernia repair, and postoperative monitoring are considered standard of care and will be the responsibility of the subject and the subject's insurance company.

ALTERNATIVES TO PARTICIPATION

Patients are under no obligation to participate in this study. A member of the research team will discuss all available surgical options with patients. It will be emphasized that refusal to participate in this study will not impact any patient's ability to receive surgical care at the Cleveland Clinic Foundation.

PAYMENTS TO SUBJECTS

There will be no payment for the subjects for the participation in this study.

POWER CALCULATION

Sample size and power calculation for this study were performed by an experienced statistician. Our primary outcome of interest on this study is to determine if Exparel® is able to decrease the total amount of opioids used during the entire hospital length of stay, especially in the first 72 hours where Exparel® should be acting. We have hypothesized that when compared to placebo, Exparel® will confer a 30% decrease in total opioid consumption during hospital stay. This was defined by clinical judgment since there is a lack of published data reporting a clinically significant reduction in opioid requirements as a consequence of other interventions. Additionally, other protocols studying Exparel® have also hypothesized that the intervention would confer the same degree of opioid use reduction. Considering a 30% reduction in total opioids consumption, an alpha of 0.05, a beta of 0.20, our study will need a sample size of 49 patients per arm to achieve a statistical power of 80%. To account for losses of follow-up during the study, we have included a 10% drop-out rate in our power calculations to anticipate the latter.

Considering a 10% dropout, the total sample size for this study will be 54 patients per arm. Therefore, the total is 162 subjects.

STATISTICAL ANALYSIS

Statistical analysis will be performed by the DDSI statistician listed in this protocol, who will determine the appropriate statistical tests for each outcome of interest. Categorical variables will be reported using proportions and analyzed using Pearson's Chi-square. Continuous variables will be reported using median and interquartile range due to their non-parametric nature and examined using either a Student's t-test or a Wilcoxon signed rank test. Pain scores,

opioid requirements, hospital length of stay, and PRQOL requirements will be compared using Mann-Whitney U tests.

PLAN FOR OBTAINING INFORMED CONSENT

Screening for eligible subjects will be performed in clinic, by the participating surgeon (PI or Co-is), during preoperative evaluation. For each subject, written informed consent will be obtained before any protocol-related activities. As part of the informed consent procedure, the principal investigator, surgeon co-investigator, or one of the approved study coordinators will explain verbally and in writing the nature, duration, and purpose of the study in such a manner that the subject is aware of potential risks, inconveniences, or adverse effects that may occur. Subjects will be informed that they may withdraw from the study at any time and will receive all information required by federal regulations.

Following identification of a potential study participant, the investigator or the study coordinator will be responsible for instituting the informed consent process in a face-to-face manner. Before starting any study procedures, the investigator will discuss the proposed research study in detail with the potential subject during the office visit to discuss treatment options. The subject will be allowed ample time to read and review the informed consent document and ask questions. The informed consent document will be reviewed with the subject in depth by the participating investigator or designated member of the research team to ensure that the potential participant has a thorough understanding of the study protocol and understands the potential risks and benefits of study participation and his or her rights as a study participant. The investigators will be available by phone or office visit to answer any questions that the participant may have.

After consideration, the subject may return if necessary for another visit with the investigator and ask additional questions before signing the informed consent document to participate in this study.

After the subject has read and reviewed the informed consent document and has agreed to participate, he/she will be asked to sign and date the document. The study member obtaining consent will also sign and date the form, and documentation of the informed consent process will be included in the research file (i.e., the person who obtained consent, where and when consent was obtained, and who was present during the process). A copy of the consent form will be given to the subject for their records.

PROVISIONS FOR SUBJECTS FROM VULNERABLE POPULATIONS

The population to be studied includes adults of at least 18 years of age. Children, cognitively-impaired persons, pregnant women, and students and house staff under the direct supervision of the investigator are considered vulnerable populations and will, therefore, be excluded from participation. If a Cleveland Clinic Foundation staff member or employee is a potential candidate for the study, the subject will be informed during the consent process that his/her participation or refusal to participate will not influence grades, employment, or subsequent recommendations .We will only enroll individuals who can fluently communicate in the English language. If a subject cannot read a consent form due to illiteracy or blindness, a member of the research study staff will read and explain the consent form to the participant or the participant's legally authorized representative. A witness who will sign and date the consent form must be present during this encounter.

SUBJECT PRIVACY AND DATA CONFIDENTIALITY

Subject anonymity and data confidentiality will be maintained throughout this study. Every effort will be made to maintain the confidentiality of documents that identify the subject by name (e.g., signed informed consent documents, clinic charts), except to the extent necessary to allow monitoring by the Office of Research Compliance at the Cleveland Clinic or by other regulatory authorities.

Much of the information collected, such as name or medical record number, will be stored in the AHSQC, a secure database that is used nationally to track clinical outcomes in patients who undergo hernia repair. Additional patient information will be recorded in RedCap®. Written consent forms and data collection forms will be stored in binders, which will stay in a locked office, at Crile Building (A10-133). Randomization will occur with the use of a customized REDCap®, a secure network/firewall-protected electronic database for which only the investigator and the designated members of the study team will have access using an individually-assigned login and password. Only approved study members listed on the IRB protocol will have access to the separately-stored master list – which will be stored in a Cleveland Clinic password-protected computer and saved on an S drive. Only the Principal Investigator, Lead Research Coordinators, and Biostatisticians will be granted access to retrieve patient data for data quality assessment and data analysis. All electronic records pertaining to the clinical study will be password-protected and only approved study members listed on the IRB protocol will have password access.

STUDY PROGRESSION / DATA SAFETY MONITORING

Progress of the study will be monitored internally by the research team. Weekly meeting between the PI, co-Is and research team will evaluate adverse events and study progression. Those will be reported to the IRB as appropriate.

CLINICAL SIGNIFICANCE/INNOVATION

This trial will be among the first to investigate the outcome of TAP blocks with Exparel® or Bupivacaine hydrochloride versus placebo through a high-quality (double-blind, 3-arm, prospective, randomized controlled trial) in the field of abdominal wall reconstruction, with outcomes considered highly relevant for patients, surgeons, and hospital administrations.

Exparel® has various theoretical reasons for reducing hospital length of stay, including decreasing the use of oral and intravenous opioids. The average cost of 24 hours of inpatient care in Ohio is $2,400-2,500 [18]. Decreasing patient's hospital stays would, therefore, afford medical systems a considerable cost advantage. However, previous studies suggesting that Exparel® may be associated with decreased hospital costs have frequently been unblinded, uncontrolled, and retrospective in nature with Exparel® packaged as part of a multimodal postoperative recovery program [19]. Such actions do not isolate the effects of each intervention and difficult to draw significant conclusions about the role of Exparel® in a multimodal pain management strategy. The outcome of this study will help to determine the role of Exparel® in postoperative analgesia of procedures with major abdominal incisions.

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